ANNALS OF INTERNAL MEDICINE

VOLUME 23 AUGUST, 1945 NUMBER 2

PENICILLIN IN SUPPURATIVE DISEASE OF THE LUNGS DUE TO *STREPTOCOCCUS HEMOLYTICUS**

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SINCE penicillin has been employed clinically only since 1941 and, until comparatively recently, has not been available in sufficient quantity to permit the study of a large series of cases, the amount of literature concerning its clinical use in suppurative diseases of the lungs is necessarily limited. There is now sufficient evidence, however, to justify its employment in pneumonia, suppurative pneumonitis, lung abscess and empyema when due to an organism or organisms susceptible to the antibiotic action of penicillin.

Although a definite decrease of empyema has occurred since the use of the sulfonamides, there is a limited group of sulfonamide resistant cases who develop empyema during the course of their treatment. Then, too, empyema may already have been present when sulfonamide was started. Tillett, Cambier and McCormack [3] found bacteria retained viability in the pleural space after sulfadiazine was injected intrapleurally. They also demonstrated the cure of empyema without rib resection when penicillin was placed directly into the empyemic cavity. Blake and Craige [4] report the successful use of penicillin in three cases of suppurative disease of the lung, due to staphylococcus in two cases and *Streptococcus hemolyticus* in the third.

Penicillin was used successfully in sulfonamide-resistant pneumonia by Bennett and Parkes.[5] They state that the results obtained in their cases represent a new phase in the treatment of empyema. Here, again, thoracotomy was obviated.

When penicillin is injected intravenously or intramuscularly, it does not penetrate in significant amounts into walled-off collections of pus such as may be found in thoracic empyema or an abscess cavity. Conversely, penicillin injected directly into an abscess does not escape rapidly.[1, 2]

* Received for publication November 20, 1944.

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One of the most remarkable properties of penicillin is its capacity to act in the presence of large quantities of pus and bacteria. On the other hand, we know that there are inhibitory substances in pus that prevent the action of sulfonamides. The use of penicillin intrapleurally may, therefore, prove revolutionary in the treatment of empyema and related pulmonary suppurative disease. This will probably be true not only in sulfonamide-resistant cases but in all cases in which the causative invading organism is susceptible to the action of penicillin.

PENICILLIN

	Diagnosis	Total Dosage	Days of Treatment	Pleural Injections	Days on Sick List
Case I	Pneumonia, *Streptococcus hemolyticus* Abscess, Pulmonary, R.L.L.	3,020,000 U.	24	0	172
Case II	Pneumonia, *Streptococcus hemolyticus* Abscess, Pulmonary, R.U.L.	1,475,000 U.	14	0	143
Case III	Pneumonia, *Streptococcus hemolyticus* Pleuritis, Suppurative, Left.	1,010,000 U.	8	8	146
Case IV	Scarlet Fever, Pneumonia, *Streptococcus hemolyticus* Pleuritis, Suppurative, Left.	1,300,000 U.	11	5	125
Case V	Pneumonia, *Strep. hemolyticus*, Multiple Lobe Pleuritis, Suppurative, Left.	2,140,000 U.	15	15	146
Case VI	Pneumonia, *Streptococcus hemolyticus* Pleuritis, Suppurative, Left.	400,000 U.	8	10	151

Hemolytic streptococcal infections respond dramatically to penicillin. However, no large number has been treated, since most of them are susceptible to sulfonamide therapy.

We report here the treatment of six cases of suppurative disease of the lungs due to the *Streptococcus hemolyticus*. Two are cases of sulfonamide resistant lung abscess following hemolytic streptococcal pneumonia. The abscesses were located in the right lower lobe (case 1) and in the right upper lobe (case 2); in case 1 there was also multiple lobe spread due to the same organism. The other four are cases of empyema following hemolytic streptococcal pneumonia, in which the hemolytic streptococcus was isolated from the pleural fluid. Two of the empyema cases were sulfonamide-resistant and the other two were in such desperate condition that the sulfonamide did not receive a fair trial preceding the change to penicillin—one has only to witness the recovery of moribund patients such as these latter to realize that we now have a drug capable of performing what a few years ago would have been termed a miracle. A predominant growth of *Streptococcus hemolyticus* in the sputum was found in all cases during the course of the pneumonia and, in cases 1 and 2, at the time the lung abscesses were

active. Cultures of the pleural fluid were positive for the same organism in the four empyema cases.

The cases of lung abscess were successfully treated with penicillin given intravenously at first, followed later by 15,000 units intramuscularly every three hours and every four hours, respectively.

In case 1 a total of 3,020,000 units was used over a period of 24 days and, in case 2 a total of 1,475,000 units over a period of 14 days. The sputum became negative for hemolytic streptococcus in cases 1 and 2 in three days and two days, respectively, after the institution of penicillin, and com-

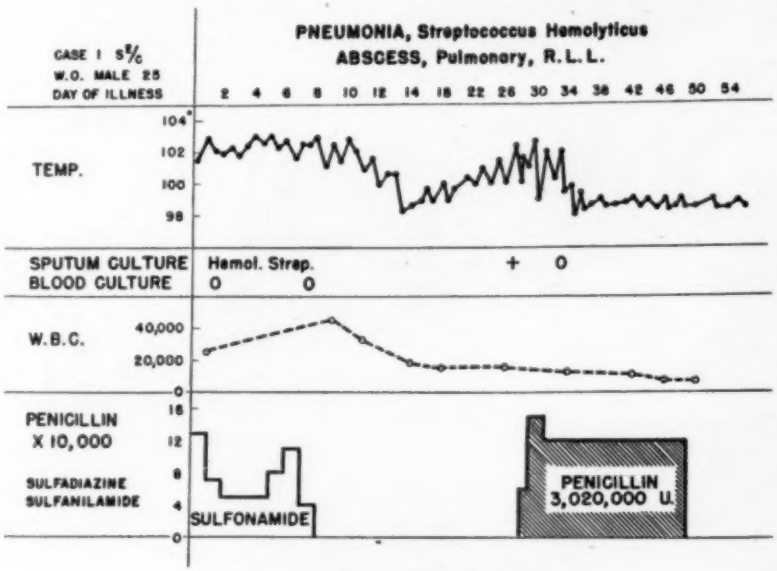


FIG. 1. Case 1, clinical record.

plete healing was demonstrated by roentgenogram in 26 and 34 days respectively. Success was probably due to the fact that these abscesses were acute and thin walled.

In the treatment of the four cases of hemolytic streptococcal empyema, intrapleural injections of 40,000 units of penicillin in normal saline solution were carried out every 12 hours during the critical stage and daily thereafter. It is true that the number of treatments given intrapleurally appears high as compared with those reported by Tillett, Cambier and McCormack,[3] who recommend 30,000–40,000 units intrapleurally on alternate days with a minimum total of three treatments. However, in view of the fact that one of eight cases they reported had recurrence and required thoracotomy, it would appear that more adequate dosage should be used.

Pleural fluid cultures were negative after the first 24 to 36 hours in all of our cases of empyema except case 6, which had 10 intrapleural injections of 40,000 units of penicillin unsupported by intravenous or intramuscular penicillin. In this instance the pleural fluid did not become negative on cul-

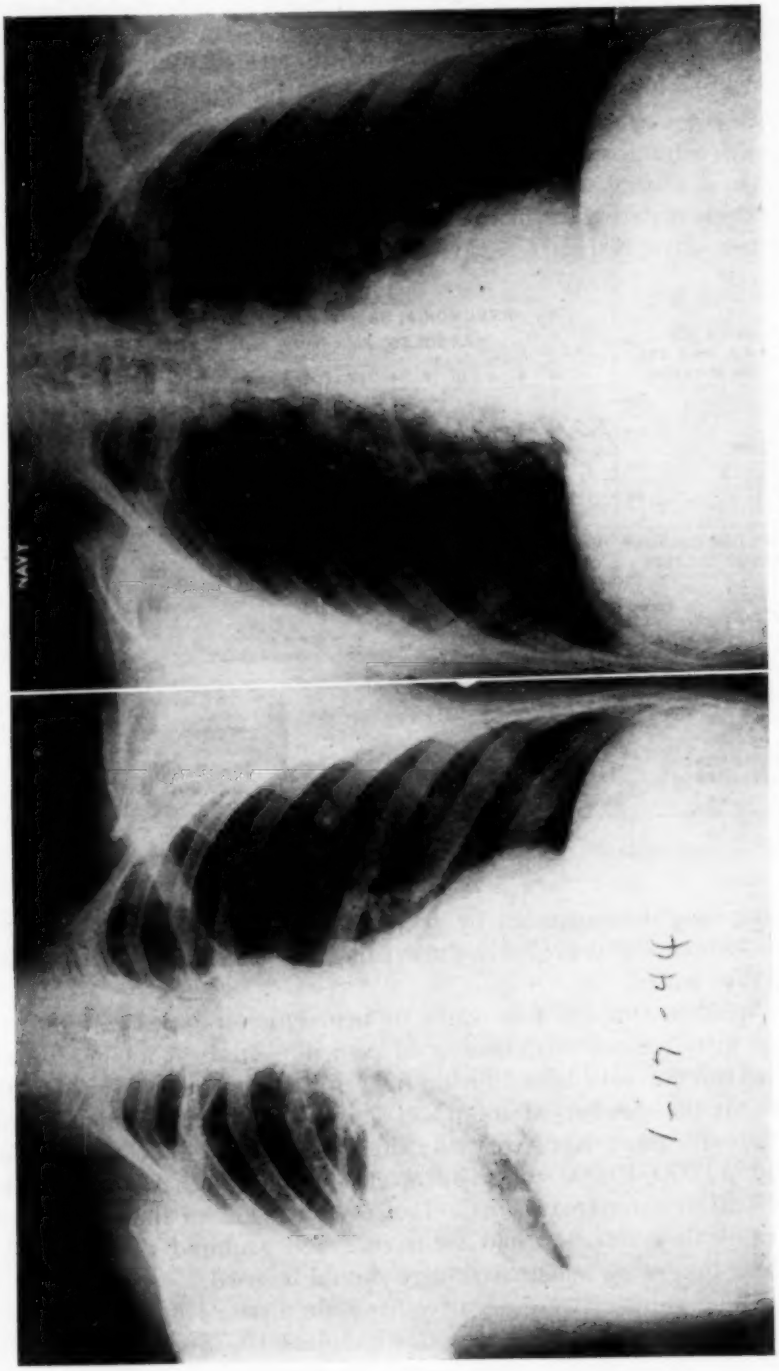


FIG. 2. (*Left*) Case 1, before penicillin therapy.
FIG. 3. (*Right*) Case 1, final roentgenogram.

ture until the sixth day, which suggests that the primary focus in the neighboring lung tissue had not been affected by the penicillin in the pleural space.

It is interesting to note that, in one of our sulfonamide-resistant cases, there was present a pleural fluid concentration of 9 mg. per cent of sulfonamide before changing to penicillin therapy, yet the pleural fluid was positive for hemolytic streptococcus on culture.

Our findings and results in this small number of cases seem to indicate that supportive systemic penicillin treatment, in addition to intrapleural injections, should be given in cases of empyema due to hemolytic streptococcus infection.

Case Reports

Case 1. W. O., male, age 25. The onset of this seaman's illness occurred 36 hours prior to admission with generalized aching, followed 12 hours later by chilliness, pain in right chest and non-productive cough. Blood culture on admission was negative. Roentgenographic examination showed evidence of consolidation in the right lower lobe and irregular patchy infiltration in the left lower lobe. Continuous oxygen therapy was necessary, as cyanosis developed when he was removed from the tent. The sputum showed a predominant growth of *Streptococcus hemolyticus.* Fifty-eight grams of sulfadiazine and sulfanilamide over a period of eight days had little effect. The white blood cell count varied from 24,500 on admission to 44,000 when sulfonamide was stopped. Following some clearing of the pneumonic process, a roentgenogram showed evidence of an abscess located at the apex of the right lower lobe, with a definite fluid level at the seventh rib posteriorly. On the twenty-seventh day following admission penicillin therapy was begun. Continuous intravenous drip was used during the first 24 hours, followed by 15,000 units every three hours intramuscularly.

The temperature, white blood cell count, and size of the cavity were steadily reduced, with rapid improvement in the general condition of the patient.

Result: There was complete healing of the abscess cavity in this sulfonamide resistant case of hemolytic streptococcal infection.

Total amount of penicillin, 3,020,000 units.

Roentgen-ray: A fine fibrous strand was demonstrable in the region of original cavity.

The patient returned to a full duty status in 172 days, which included convalescent care and light duty before discharge from hospital.

Diagnosis: Pneumonia, lobar, multiple lobe; abscess, pulmonary, right lower lobe, *Streptococcus hemolyticus.*

Case 2. D. L., male, age 21. This 21 year old seaman was admitted to the hospital on December 19, 1943. His present illness began one week prior to admission with a sore throat, followed by malaise and generalized aching. He became progressively worse and 24 hours prior to admission had nausea, vomiting and chills. Physical examination revealed a temperature of 105° F., pulse of 120 and respirations 34, and the roentgenogram revealed consolidation of the right upper lung field. He appeared acutely ill but had little pulmonary embarrassment, and he responded slowly to sodium sulfadiazine and sulfanilamide. His temperature reached normal on the tenth day and then began spiking daily to 102° F., with pain on coughing over right upper anterior chest. On January 3, 1944, the roentgenogram revealed some clearing centrally but also a small rounded area of increased radiolucency at the third anterior interspace, which was somewhat suggestive but not diagnostic of abscess cavity. Repeated sputum examinations continued to show *Streptococcus hemolyticus* predominant on culture. By January 5, 1944, his temperature reached 104° F., and

respirations were 26. White blood cell count again rose to 16,000 with 84 per cent polymorphonuclears. On January 5, 1944, penicillin therapy was begun, 5,000 units being given every hour by the intravenous route. This was followed by 15,000 units intramuscularly every four hours day and night, with a total dosage of 2,140,000 units of penicillin over a period of 14 days. On the day penicillin therapy was started, a roentgenogram of the chest showed that the area of increased radiolucency appeared larger than when first noted, measuring 3 cm. in diameter, with a fluid level. Four days after the institution of penicillin therapy, temperature reached normal and remained so except for slight spiking to 99.6° F. The sputum, which had been repeatedly positive for *Streptococcus hemolyticus,* became negative in 48 hours after the institution of penicillin and remained negative thereafter. Recovery was rapid, and on April 10, 1944, roentgenogram showed only a minimal amount of residual infiltration in the area of the former abscess. The patient returned to a full duty status on April 12, 1944. A roentgenogram after return to duty showed only a small fibrous strand in the area of the former abscess.

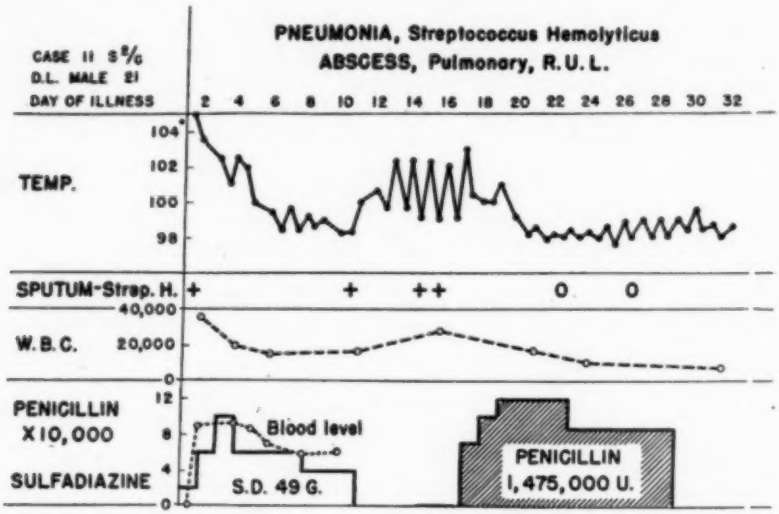


FIG. 4. Case 2, clinical record.

Résumé: This is a sulfonamide-resistant case of pneumonia, lobar, *Streptococcus hemolyticus,* showing repeatedly positive sputum cultures until 48 hours after penicillin therapy was instituted. The abscess which developed in the right upper lobe apparently was sufficiently thin walled to have absorbed the drug.

Total dosage: 1,475,000 units over a period of 14 days.

The patient returned to full duty status in 143 days.

Diagnosis: Pneumonia, lobar, right upper lobe; abscess, pulmonary, *Streptococcus hemolyticus.*

Case 3. W. M., male, age 19. This patient was admitted with complaint of pain in left chest of two days' duration, requiring a hypodermic for relief while in the dispensary. He had a severe cough but no hemoptysis.

Temperature was 102–103° F., white blood cells numbered 34,000 and the sputum showed predominating growth of *Streptococcus hemolyticus.* After 59 grams of sulfadiazine over a period of six days, this case was considered to be sulfonamide-resistant. The patient continued to run a septic temperature, with a leukocytosis of 16,900, and signs of fluid were present over the left lower chest. Aspiration revealed

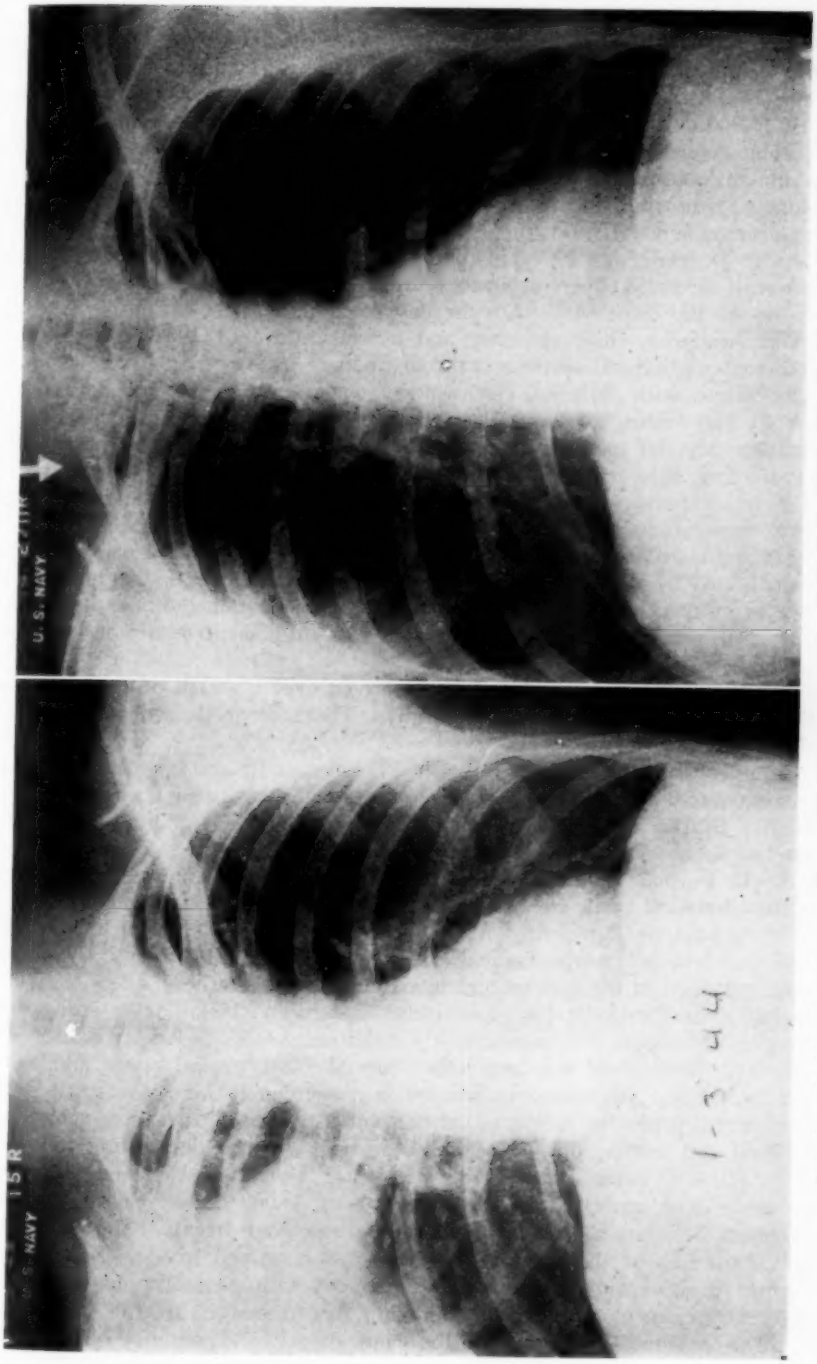


FIG. 5. (*Left*) Case 2, roentgenogram before penicillin therapy and after 49 grams of sulfonamide.
FIG. 6. (*Right*) Case 2, final roentgenogram.

240 c.c. of cloudy pleural fluid. The culture was positive for *Streptococcus hemolyticus* in 24 hours and penicillin therapy was begun.

A total of 1,010,000 units of penicillin was given over a period of eight days: 320,000 units (eight injections of 40,000 units each) were injected into the intrapleural space within six days, and the remaining 690,000 units were given by intramuscular injections of 15,000 units every four hours day and night for eight days.

The patient returned to full duty status in 145 days. There was no residual pleuritis or fibrosis, and thoracotomy was obviated.

Diagnosis: Pneumonia, lobar, *Streptococcus hemolyticus;* pleuritis, suppurative, acute, *Streptococcus hemolyticus.*

Case 4. P. D., male, age 19. This patient was admitted to the hospital 10 days after the onset of an acute upper respiratory infection, for which he spent seven days in the sick-bay of the dispensary. On the day of admission to the hospital he developed severe headache, chill, vomiting and a temperature of 103° F. A diffuse erythematous rash and typical scarlatinal throat findings were present. His condition grew rapidly worse, with delirium, restlessness, temperature of 105° F., pulse 150, respirations 40, and findings of consolidation in his left lower lobe. Sodium sulfadiazine intravenously and sulfadiazine by mouth resulted in no change in the patient's condition in the first 24 hours. Signs of fluid were present at this time, and aspiration revealed cloudy seropurulent fluid which on culture showed an abundant growth of *Streptococcus hemolyticus.*

Daily tap and instillation of 40,000 units of penicillin for five doses was supported by 5,000 units hourly by intravenous route for 24 hours, followed by 15,000 units intramuscularly every four hours day and night. A dry tap was obtained on the eighth day.

Résumé: Sulfonamide therapy at the outset was insufficient to demonstrate this case sulfonamide-resistant.

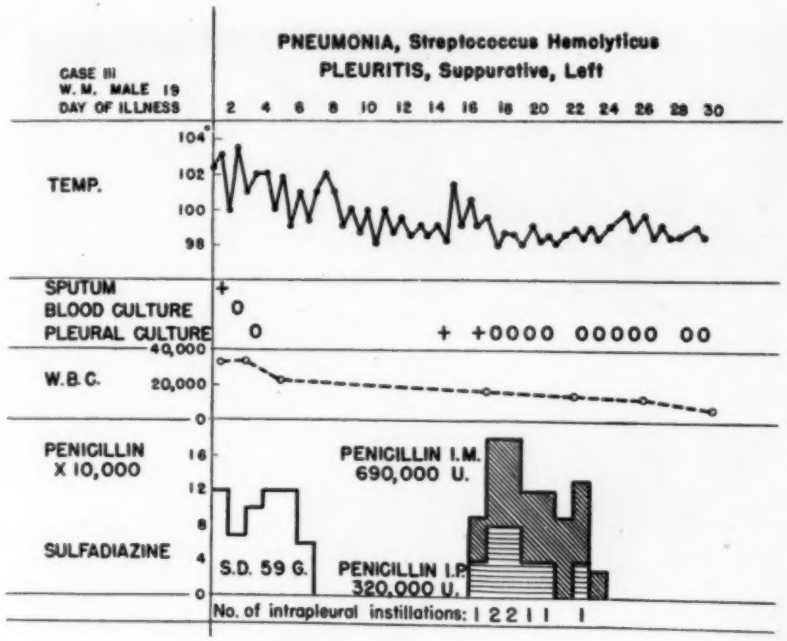
A total of 1,300,000 units of penicillin was given over a period of eight days, of which 200,000 units were injected intrapleurally. Thoracotomy was obviated in this case.

The patient returned to full duty status in 125 days, and check-up roentgenograms taken after return to duty showed no evidence of residual pleuritis or fibrosis.

Diagnosis: Scarlet fever and pneumonia, lobar; pleuritis, suppurative, *Streptococcus hemolyticus.*

Case 5. D. P., male, age 18. The onset of this seaman's illness occurred three days prior to admission while he was en route from a coastal station. Cough and severe left chest pain were present, with temperature of 105° F., leukocytosis of 42,000 with 87 per cent polymorphonuclear cells. *Streptococcus hemolyticus* was the predominant organism in the sputum and blood culture was sterile.

Following sodium sulfadiazine given intravenously and sulfadiazine orally, continuous oxygen and supportive measures, his condition was considerably worse. On the second day, cloudy fluid was aspirated from the left pleural space and found positive on culture for *Streptococcus hemolyticus,* whereupon there was started continuous intravenous penicillin in normal saline solution. In addition, three aspirations of pleural fluid and instillations of penicillin were performed during the following 24 hours, 40,000 units being injected following each aspiration. The next day two aspirations were done, each followed by injection of 40,000 units. Culture of fluid and direct smear 24 hours after starting this treatment were negative for organisms. Subsequently, cultures of the pleural fluid aspirated remained sterile. Sputum cultures remained positive and intramuscular treatment with penicillin, in support of the intrapleural treatment, was given following discontinuance of the intravenous penicillin. The pneumonic process in the right upper and middle lobes cleared quickly, but residual findings of fluid in the left pleural space necessitated a total of 15 aspirations and a similar number of penicillin instillations.



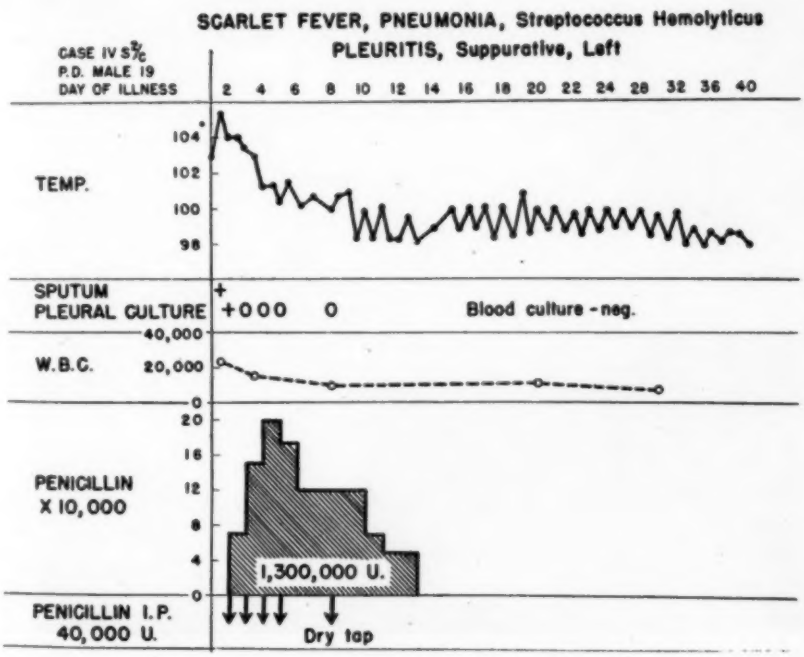


FIG. 7. (*Above*) Case 3, clinical record.
FIG. 8. (*Below*) Case 4, clinical record.

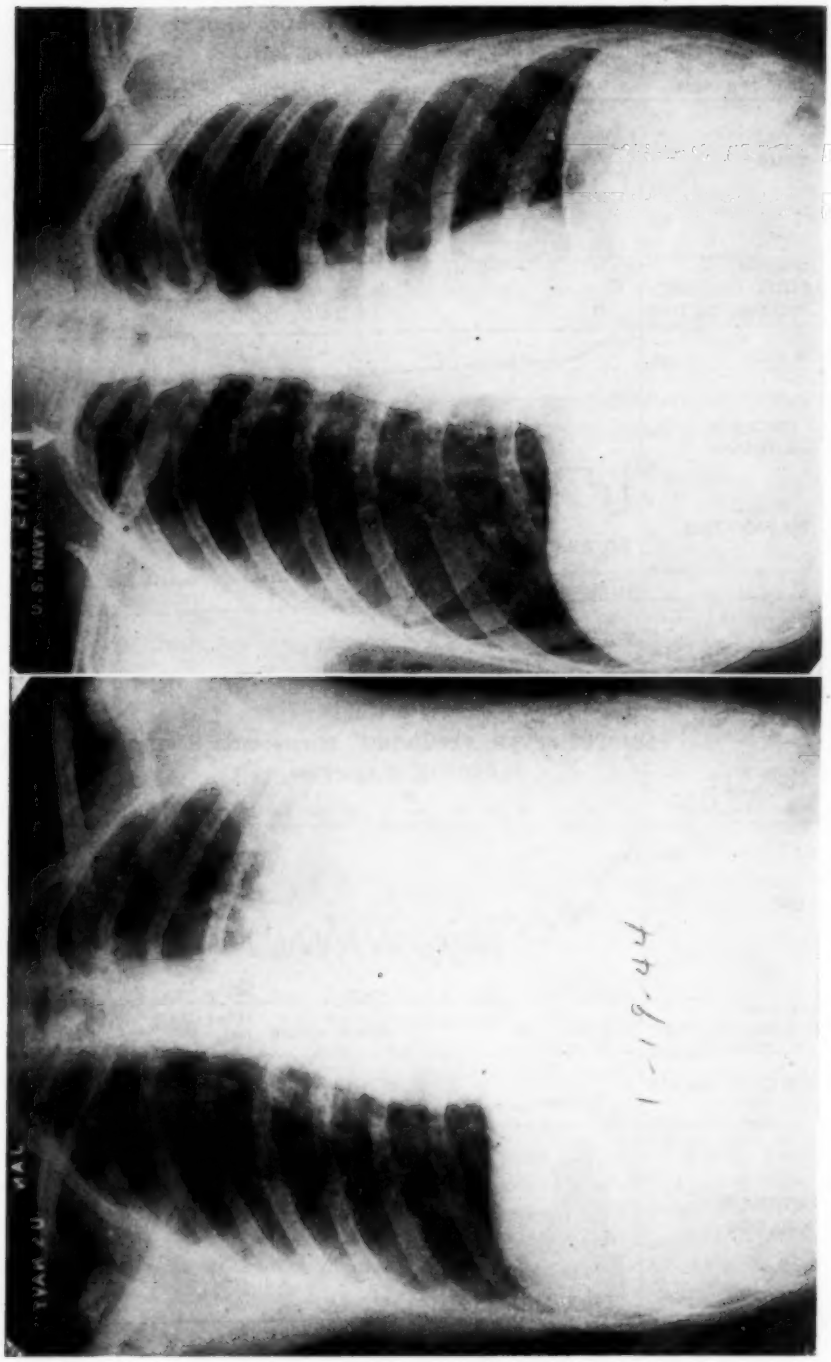


FIG. 9. (*Left*) Case 4, roentgenogram taken during course of penicillin therapy.
FIG. 10. (*Right*) Case 4, final roentgenogram.

Résumé: This patient returned to full duty status after 151 days on the sick list. Final roentgenogram on discharge from the hospital showed residual slight pleural thickening, diaphragmatic blunting and obliteration of the costophrenic sulcus.

A total of 2,140,000 units of penicillin was given, of which 600,000 units were injected intrapleurally in 15 doses of 40,000 units each.

Sulfonamide therapy at the outset was insufficient to demonstrate this case sulfonamide-resistant. The desperate condition on the second day warranted a change of treatment.

Diagnosis: Pneumonia, lobar, multiple lobe, *Streptococcus hemolyticus,* and pleuritis, suppurative, acute, left.

Case 6. F. Z., male, age 19. The patient was admitted to the hospital with a history of cough, chill and knife-like pain in the left lower chest. Physical findings of consolidation were supported by roentgenographic findings of consolidation of the left lower lobe. The original roentgenogram showed narrowing of the intercostal spaces on the left with increased obliquity of the ribs on this side. Sputum culture before sulfonamide therapy showed predominant growth of *Streptococcus hemolyticus.* The blood culture was negative.

Past history showed repeated chest and upper respiratory infections from the age of four. At times these were followed by asthma.

Clinical course showed a poor response to intravenous sodium sulfadiazine followed by sulfadiazine orally. A total dosage of 86 grams of sulfonamide was given over a period of 17 days. Signs of fluid developed and on the first aspiration it was clear and negative on culture. Temperature and leukocytosis persisted, and the second aspiration was cloudy and showed a good growth of *Streptococcus hemolyticus.*

Penicillin therapy was given only by the intrapleural route. Daily aspiration with instillation of 40,000 units of penicillin was followed for a period of eight days; on two of these days, 80,000 units were given by injections 12 hours apart. The cultures of the pleural fluid remained positive for organisms for five days after daily instillations of penicillin intrapleurally. Temperature returned to normal the twenty-first day and remained so. A thin layer of pleural fluid was found on tapping after penicillin had been discontinued. This proved negative on culture.

Résumé: Sulfonamide-resistant case of pneumonia, lobar, *Streptococcus hemolyticus,* and complicating pleuritis, suppurative. Four hundred thousand units of penicillin were given by 10 intrapleural instillations of 40,000 units.

The patient returned to a limited duty status in 151 days because of slight dyspnea on severe exertion. The initial roentgenogram suggests the possibility of previous lung parenchymal damage and fibrosis.

Penicillin given only intrapleurally failed to sterilize the pleural space until the sixth day. Other cases having supplemental intravenous and intramuscular penicillin therapy were never positive after 36 hours.

Diagnosis: Pneumonia, lobar, *Streptococcus hemolyticus;* pleuritis, suppurative.

Conclusions

1. Two cases of lung abscess resulting in the course of sulfonamide-resistant *Streptococcus hemolyticus* pneumonia were successfully treated with penicillin parenterally. The number of days of penicillin therapy, 14 and 24, and the total dosage of 1,475,000 and 3,020,000 units are indicative of absorption of penicillin through thin walled cavities when treated over a sufficient period of time.

2. The sputum in the two cases of lung abscess became negative for hemolytic streptococcus in three days and two days respectively. Complete

healing, demonstrated by roentgenogram, occurred in 26 and 34 days, respectively.

3. Four cases of *Streptococcus hemolyticus* empyema were successfully treated by intrapleural injection of penicillin supported by intravenous and intramuscular use of the drug. Two of these cases were classified as sulfonamide-resistant and the other two had insufficient sulfonamide to be classified as such. The latter were moribund.

4. Thoracotomy was obviated in all cases of empyema.

5. No evidence of reinfection or recurrence has occurred in any of these cases.

6. Aspirated pleural fluid remained sterile after 24 to 36 hours, when the intrapleural treatment was supplemented by intravenous and, later, by intramuscular penicillin. The case receiving only intrapleural penicillin retained an infected pleural space until the sixth day after treatment was started. Success or failure may hinge upon the supplemental parenteral administration of penicillin.

7. Residual fibrosis and subjective slight dyspnea necessitated return to a limited duty status in one case. This seaman had had repeated infections with periodic asthma since the age of four. The three other cases returned to a full duty status in 125, 146 and 151 days, respectively.

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UPPER RESPIRATORY INFECTIONS: A RÉSUMÉ OF RECENT PERTINENT DATA AND OBSERVATIONS OF INCIDENCE ABOARD A DESTROYER *

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THE recent emphasis by many observers that upper respiratory infections constitute a very important cause of incapacitating man power prompted the present study aboard a destroyer. The comparative incidence of such infections at sea and in port or where there were other opportunities for contact formed an added feature of interest. As the scope of this subject matter is rather diverse, it seems pertinent primarily to review the varied component features.

I. GENERAL CONSIDERATIONS

The term "upper respiratory infections" is a thoroughly non-specific one and includes the common cold, catarrhal fever, influenza or "flu," acute pharyngitis, and tonsillitis. Although these various entities are quite unrelated as to etiology, they are similar in their epidemiology and pathology, and in the fact that together they form the most important factor in loss of time in industry and in the military services, as recently stressed by Keefer.[1]

A. Statistics. In a survey of absenteeism in 11,446 munitions workers in England, Massey and Pearson [2] found that 50 per cent of all male workers and 45 per cent of all female workers lost some time due to illness (in a period of six months); colds and influenza resulted in 23.7 per cent of the sick absences among males and 24 per cent among females, the greatest time waste due to any single group of illnesses. In the United States Navy, Smiley [3] has pointed out that since 1881 the median rate for colds and sore throat has been 2,500 per 1,000 per year, and for more severe respiratory infections (influenza, etc.) 86.9 per 1,000 per year. At a west coast shore station during a period of four summer weeks, 130 of 7,500 individuals were sick enough with catarrhal fever to require bed rest.[4] It is clear then that the illnesses included in the term "upper respiratory infection" actually do constitute a definite group. As such, they assume importance by virtue of their prevalence and the fact that they are "saboteur No. 1" in producing time loss in industry and in the military services. For these reasons, it is felt that any observations, however insignificant, should be recorded in the hope of further building up the facts concerning this group and thereby eventually eliminating their effects on manpower.

* Received for publication December 6, 1944.

B. Diagnosis. Although it seems permissible to deal with these diseases as a group, they should nevertheless be sharply delineated in the diagnosis of individual cases. Since they are similar in many of their manifestations, differential diagnosis is indeed difficult, though not impossible as pointed out by the Naval Laboratory Research Unit No. 1,[5] by Smiley,[3] and by Keefer.[1] The clinical picture is probably most significant in making a correct diagnosis, although laboratory aids are at hand, such as the identification of etiological agent in some instances by culture or animal inoculation, immunological or serological reactions including cold agglutinations in atypical pneumonia and blood counts. The therapeutic response to sulfonamides may also empirically suggest a group entity. When all other means seem inconclusive, clinical course and reasoning by a process of elimination may help to clarify the problem of diagnosis. The important point is that all who handle these cases should realize that differentiation is possible and earnest efforts should be made to be accurate in diagnosing these conditions. Only in this way can the problems concerning them be further clarified.

C. Pathology. The pathological aspects of these infections have been clearly and concisely presented by Warren.[6] From his descriptions, it is seen that the pathological differences are largely ones of degree rather than kind, being more severe in some with the outpouring of exudates, and mild in others with only hyperemia, congestion, and edema. Mucosa, submucosa, and underlying connective tissue are involved by the severe, invasive processes, whereas only the mucosa is involved in the mildest infections. Such a sequence of the pathologic lesions is a very graphic indication of the well-established belief that the etiological agents of these infections gain entrance through the nose or mouth. They settle on the mucosa of the respiratory tract and, other factors not being unfavorable for them, they proceed to multiply and invade the local tissues reaching various depths in accordance with their virulence. Some etiological agents, as a type, are usually mild (that causing the common cold) whereas others are vigorous (various streptococci). From this fact, the pathological condition which they evoke does suggest them by its degree, though not infallibly, since there is indeed a wide range of degrees of reaction to any one of these agents. Their similarity pathologically appears further to justify the consideration of these infections as a group.

D. Complications. The possible complications and sequelae of this group are numerous and important, varying from peritonsillar abscess to pneumonia, septicemia, arthritis, meningitis and nephritis. When complications do occur, they far outstrip the primary infection in morbidity and in causing loss of time. These facts give further prominence to upper respiratory infections. Measures by which complications might be prevented are naturally brought to mind. Sulfonamides have been found to be of little efficacy in the treatment of catarrhal fever,[4] or of "simple respiratory tract infections."[7] However, their use both locally[8,9] and by mouth is often recommended for the prevention of complications, particularly sinusitis,

pneumonia, etc. Their usefulness in the treatment of these complications (pneumonia, meningitis, septicemia, etc.) is undisputed. However, as Keefer [1] points out, there are needed adequate and effective chemotherapeutic agents for the treatment of the primary infections. It appears doubtful that penicillin will serve this latter purpose.

II. Etiology and Epidemiology

A. The Causative Agents. The types of agents involved in these diseases are varied. Some are viruses, as in the common cold and influenza; some are staphylococci or streptococci, *H. influenzae* or pneumococci; others are ill-defined as in catarrhal fever.

B. Transmission. All of these agents are presumably transmitted by the respiratory route as a result of direct contact with the patient (droplet infection) or with a healthy carrier. That carriers do occur in this group is well known and widely accepted, particularly in reference to those infections caused by streptococci, staphylococci, and pneumococci. Occasionally, especially in the case of streptococcus, milk may form the vehicle. A recent survey by Silverthorne and Patterson [10] indicates a scarcity of carriers of *H. influenzae*—only one child was positive out of 55 children and 62 adults checked by nasopharyngeal culture.

C. Immunology. The concept of healthy carriers implies that some persons have an immunity to the infections in question. The existence of immune bodies for streptococci, staphylococci, and pneumococci is well established. The immunological properties of the influenza virus are less clear but are being rapidly elucidated. In an investigation of an influenza epidemic in military camps in Australia, Burnet et al.[11] noted that patients showed a sharp rise in antibody titer against the current strain of influenza virus in two weeks following the illness, whereas blood samples taken during the first few days of illness were much lower in antibody than were samples from normal subjects. Similar rises in antibody titer following influenza infections have been reported by Eaton and Martin.[12] Subcutaneous vaccination with both active and formalinized influenza virus preparations have also resulted in increasing the antibody titer both in blood serum [13] and in nasal secretions.[14] The work of the personnel of the Naval Laboratory Research Unit No. 1 [15] in this regard dealt with a group of about 10,000 vaccinated and 10,000 unvaccinated (control) individuals and should, therefore, be quite conclusive. Vaccination by intranasal inoculation with living attenuated influenza virus (both A and B strains) also produced a significant rise in antibody titer in most patients.[15, 16, 17] According to Burnet,[16] this rise was most marked among those with lower initial antibody levels. The simplicity of the intranasal route, demanding less manpower, material, and time, makes it particularly inviting and the results especially significant.

It is stated by Bodily and Eaton [18] that there exists only a limited amount of antibody-specificity for strains of influenza A infection and in persons

vaccinated with influenza A vaccine. They consider that wide variations exist in the specificity of immune response of human subjects to any given strain of influenza virus. The Naval Laboratory Research Unit No. 1 [13] also points out that, whereas these serological data are of interest, they do not necessarily prove that the development of antibodies implies existence of actual immunity against influenza. In view of the facts regarding this matter in other diseases, however, it is reasonable to assume that there is a direct proportion between immunity and antibody titer. By way of demonstrating the correctness of this assumption, Henle et al.[19] subjected a group of persons immunized with formalin-inactivated influenza vaccine and a group of untreated control individuals to inhalation of an active influenza A virus. They found that the antibody level before inhalation and the degree of protection from infection were directly proportional, those with the lowest antibody titers developing a clinical form of influenza, those with the highest titers being unaffected by the inhalations.

The existence of an influenza receptolysin is commented upon editorially in the *Journal of the American Medical Association*.[20] The work of Hirst [21] on the absorption of influenza virus on cells of the respiratory tract is noteworthy in this regard.

The immunology of influenza is thus being clarified. With others (catarrhal fever, common cold) of the group of upper respiratory infections, the picture is less well-defined. Considerable work on "cold vaccines" has been reported. Most of this is in accord with the study of Siegel et al.[22] who found no significant differences with regard to incidence, severity, or complications of colds between 120 controls and 125 experimental subjects, when a trial of "oral cold vaccine" was made.

D. Vitamins. The part played by vitamins in relation to this group of infections seems entirely non-specific. A two year controlled study by Cowan, Diehl, and Baker [23] of 774 college students on adequate diets indicates that the daily administration of multivitamin capsules did not significantly decrease the incidence, duration, and severity of colds. On the other hand, the use of vitamin concentrates, particularly vitamin C,[24] is probably of value during and after these illnesses. Thus, vitamins are no more important in upper respiratory infections than they are in any other infectious process. If the diet is primarily adequate, nothing is gained by an excessive vitamin intake.

E. Meteorology and Added Factors. A very important consideration in the epidemiology of upper respiratory infections is the relationship of weather, climate, and other environmental and situational factors. That such a relationship does exist is indicated by the various peaks of incidence of common colds in the United States (in January and February, April and May, September and October). An article by Mills [25] dealing with the general effects of climate upon disease is of interest here. The relationship certainly would seem logical since all vitality factors must have their functional basis

in energy liberated from tissue combustion, and the tissue combustion level is directly influenced by climate. Laboratory studies by Mills have shown that ability to fight infection is definitely higher under conditions that facilitate body heat loss than where heat loss is difficult. Thus, antibody production after typhoid vaccine injection into rabbits is almost twice as great in animals kept at a lower temperature. Locke [26] also provided support for the idea that combustion level is an important factor in determining resistance to infection. He found that the ability of animals to survive pneumococcus infection (by inoculation) or of human beings to maintain freedom from respiratory infection was related to their rate of oxygen utilization.

In addition to the effect of temperature alone, the storminess of a season, atmospheric pressure changes, and sudden chilling of the body seem in some manner related to the initiation of the infectious disease attacks.[25] The upper respiratory infections are most closely involved in this type of climatic effect. Thus, the summer freedom from respiratory infection is attributable in very large part to the lessened storminess of that season and the greater freedom from sudden body chilling. In the United States, the increased mortality from respiratory infections from summer low to midwinter high is three times that in Australia, though the latitudes of the countries are similar. The unusually stormy winters with great atmospheric turbulence in the United States are held accountable for this fact. Climatic and weather influences, therefore, are of great importance among the outside forces bearing on the patient's welfare and health.

Of particular interest are the observations of Paul and Freese [27] on the common cold in an Arctic community isolated in winter. They found that apparently an unfavorable environmental factor, such as a sudden drop in atmospheric temperature, was not necessary for the development of an epidemic of colds. The arrival of the first boat of the shipping season, however, was usually followed by an epidemic involving the whole community in a short while. This suggests, as they say, that the introduction of the virus from the outside is more important than the climate. Also, trappers who fell through the ice did not develop colds during the winter and spring but did so if this happened after the men had been to town in the summer and fall. Thus, sudden chilling of the body may bring on an attack in a person who has had a recent infection or a recent contact, but only if such a condition accompanied the chilling.

Outbreaks of colds were noted by Paul on the "Carnegie" when the ship entered a cold current from warmer waters even though it had been out of port for days or weeks. This suggests that exposure to cold may in some way activate the virus in a group after it has failed to produce infection for many days or weeks preceding the outbreaks. According to Paul, it seems plain that a more careful definition of the host and environmental factors which favor the invasion of the virus of the common cold is necessary before the spread of the infection can be effectively controlled.

III. The Upper Respiratory Infections Aboard a Destroyer

No doubt the medical officers of other warships in our zone have observed the same factors as herein noted. If so, the significance of our observations will be greatly increased, for as it stands the personnel of one destroyer accounts for only a few hundred men among the thousands of individuals who are now living under similar conditions.

Table I

Incidence by Months of 607 Visits to Sick-Bay for Various Upper Respiratory Diseases

Months:	Visits to Sick-Bay:	Months:	Visits to Sick-Bay:
December	126	October	3
January	16	November	12
February	45	December	2
March	120	January	40
April	20	February	8
May	56	March	1
June	4	April 1–15	3 (15)
July	5	April 15–30	12 (15)
August	28	May	12
September	6	June	88

Compare with figure 1.

Table II

Incidence by Months of 61 Admissions to Sick List for Various Upper Respiratory Diseases

Months:	Number of Admissions to Sick List:	Months:	Number of Admissions to Sick List:
December	8	October	0
January	2	November	0
February	4	December	0
March	22	January	2
April	3	February	0
May	12	March	0
June	2	April	0
July	0	May	0
August	1	June	5
September	0		

Compare with figure 2.

Table III

Various Diagnoses in Cases of Upper Respiratory Infections Admitted to Sick List Over a Period of 19 Months

Diagnosis:	Number of Cases:
Bronchitis, acute	3
Catarrhal fever, acute	24
Influenza	0
Laryngitis, acute	1
Pharyngitis, acute	16
Septic sore throat	1
Tonsillitis, acute	15
Tracheitis, acute	1

The personnel of a ship at sea constitutes in effect a mobile, isolated community; a small community it is true, when we are speaking of a destroyer. That isolation is maintained as long as the ship remains at sea or, at least, does not have contact with persons ashore, particularly persons

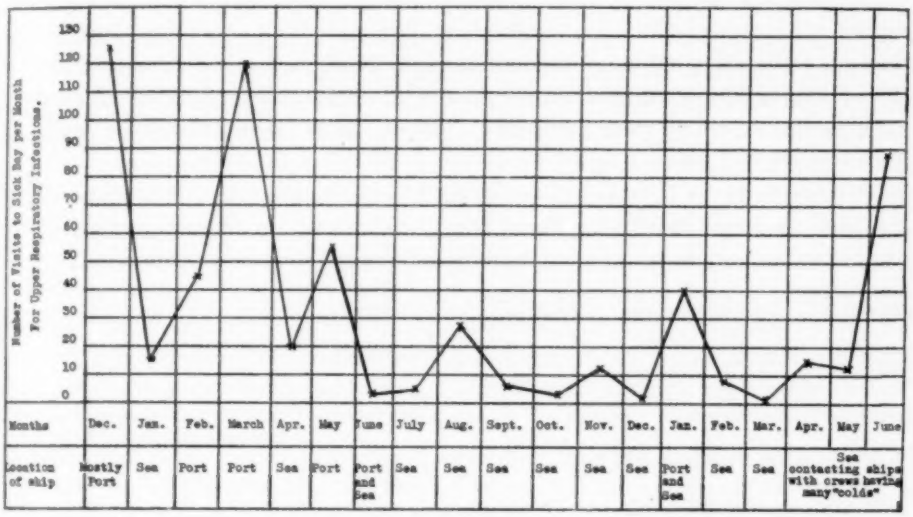

FIG. 1.

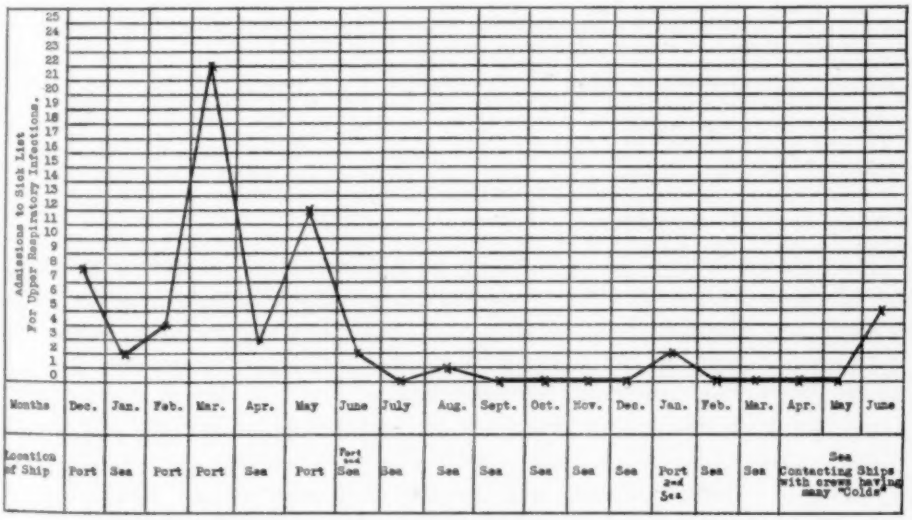

FIG. 2.

organized into communities. Additional points in regard to individuals living aboard warships, particularly destroyers, are the closeness of their quarters and the crowding into small spaces. By this it is implied that as far as respiratory tract infections are concerned among these individuals, it is

"all for one and one for all"; i.e., contact is sufficiently close that nearly all men are exposed to one another and what respiratory infection one has, will be spread to all aboard who are susceptible.

With these points in mind, the following facts are presented:

During a period of 19 months, there was a total of 607 visits to the sick-bay of this ship for upper respiratory infections of varying degrees of severity. Of these 61 were severe enough to require admission to the sick list; i.e., those whose illnesses were febrile and who required relief from duty for a period of more than 24 hours. These facts are indicated in tables 1, 2, and 3 and in figures 1 and 2.

Although it is impossible to indicate specifically the data concerning the ship's movements during this time, the circumstances surrounding these marked variations in respiratory infections aboard may be presented:

December:	Temperate zone. Mostly in port.
January:	Tropics. At sea.
February:	In the north. In port.
March:	In the north. In port.
April:	Temperate zone. At sea.
May:	In the north. In port.
June:	Temperate and tropical zones. Partially in port and partially at sea.
July:	Tropical zone. At sea.
August:	Tropics. At sea.
September:	Tropics. At sea.
October:	Tropics. At sea.

November:	Tropics. At sea. Fatigue.
December:	Tropics. At sea. Severe fatigue.
January:	Tropical and temperate areas. At sea and in port. Rest.
February:	Tropics. At sea. Fatigue.
March:	Tropics. At sea. Mild fatigue.
April:	Tropics. At sea. Increased contact with other ships about 15th.
May:	Tropics. At sea. Increased contact with other ships.
June:	Tropics. At sea. Contact with ship having many "colds" aboard.

Along with fatigue during the months of November, December, February and March were also conditions which made dietary factors irregular with possibly low vitamin intake, lack of milk and fresh vegetables. There was great loss of sleep on the part of all hands, and opportunities for bathing were at fairly wide intervals (two to three days). Also during much of this period, the personnel were frequently wet with profuse rains. The factor of body chilling, however, was usually absent. Beginning with the latter part of April there was increased contact with other ships. One of these ships (in June) had a large number of men aboard with "colds."

Comments

By comparing these circumstances with the figures and graphs showing incidence of upper respiratory infections, it is readily seen that there is a close relationship between contacts with the shore and increased number

of respiratory infections. Thus, there are peaks in December, February-March, May and January. There is a slight elevation of incidence in August. This is not completely understood. There was considerable fatigue during this month, to which the personnel may not yet have become adapted. Otherwise, such factors as fatigue with its usually discussed "lowered bodily resistance," irregular dietary and bowel habits, impaired sanitation measures (bathing, etc.), wetting of body surface by rains, etc., all seemed to be without effect in bringing about an increased incidence of upper respiratory infections when adaptation to these factors had occurred. These observations are in accord with those of Paul and Freese[27] concerning Spitsbergen, and suggest that the introduction of the infectious agents by outside contacts is the important factor in initiating increased incidence of these diseases. Also, since incidence seems to fall off so abruptly (within two weeks or so), "carriers" among our own personnel were apparently of no significance, owing either to the short period of survival or of infectiousness of the causative agents which they might have carried, or to a possible, though rather far-fetched, conception of an inter-immunity of the personnel, each to whatever agents his fellows might carry. In regard to this latter, though several groups of healthy individuals were received aboard during the months of July through December, none of them seemed to fall victim to any of our possible agents, nor did their arrival bring about a definite outbreak among the personnel aboard. It is possible that the slight increases noted during April and May were due to this fact, for most of the new personnel arrived during these months. There is quite a definite rise in admissions to sick list and visits to the sick-bay in June. It is felt that these upper respiratory infections had their origin in contact with another ship whose personnel had numerous "colds."

Summary and Conclusions

Upper respiratory infections have been dealt with as a group, taking into account their statistical importance, differential diagnosis, pathology, complications, and epidemiological considerations. The facts concerning the incidence of these infections aboard a destroyer and the various conditions of climate, etc., surrounding them are presented. It has been noted that outside contacts (with persons ashore, in other ships, etc.) are apparently the most important factor in bringing about an outbreak of these infections. Without such contacts, within a period of two to three weeks (or less), upper respiratory infections tend to diminish progressively, approaching an extremely low level. This seems important, since if such can happen in a small "community" (the personnel of a destroyer), it can possibly be brought about ashore in larger communities.

In consideration of factors which may have allowed the relative disappearances and later produced reappearances of upper respiratory infections aboard, the following statements are made:

(1) Outside contacts bring about increased incidence. In the absence of outside contacts, respiratory infections tend to disappear within two to six weeks.

(2) In general, no sudden, severe climatic changes were encountered. Gradual changes of this nature apparently have little or no influence on the problem.

(3) In the absence of contacts, such adverse factors as long continued fatigue (to the point of exhaustion), monotony, irregular and possibly slightly deficient (qualitatively) diet, loss of sleep, inaccessibility of bathing facilities, seem to be of no importance.

(4) These observations serve to confirm the significance of "contacts" for this group of infections. Furthermore, the "set-up" (viz: mobility and interval environmental changes) afforded the analogue of serial experimental observations. Through this available means the importance of "contact" is emphasized, while that of such factors as fatigue, loss of sleep, exposure and the like is minimized. Thus, stated simply, though most difficult to put into practice, the control of this important group of diseases seems to lie in the control of "contacts."

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THE FUNCTIONAL CONSEQUENCES OF CORONARY OCCLUSION *

By Carl J. Wiggers, M.D., D.Sc., F.A.C.P., *Cleveland, Ohio*

The symptomatology of acute coronary occlusion is too well-known to require detailed redescription. Let it suffice for our purpose to recall three outstanding phenomena, so serious for the patient and so informative for the physician in formulating a diagnosis: *1,* the agonizing pain, crescendo in character and radiating from a focal region over the sternum outward to the left arm, upward to the throat, and downward to the epigastrium; *2,* the irregular or rapid action of the heart; and *3,* the signs of cardiovascular failure, such as hypotension, feeble pulse, venous congestion, cutaneous pallor, sweating, cyanosis, etc., which frequently raise the questions as to whether circulatory failure is of central or peripheral origin and whether the diagnosis of circulatory collapse or shock is warranted. It is with functional conditions leading to these signs and symptoms *during an attack* rather than with those which prove immediately fatal or those which persist after recovery that my discussion is chiefly concerned. Pathological studies have not shed much light upon this stage of coronary occlusion except through speculative inferences, whereas experimental studies—mostly on dogs—have revealed the nature of the functional disturbances and furnished us with the guiding principles in interpreting the clinical symptomatology, in formulating a prognosis and, in some instances, in directing our therapeutic trends. I venture to analyze some of these early functional changes, because it has been my privilege to carry out many experiments pertaining to these problems myself, to direct others in my laboratory and to witness still others of colleagues in our school—an experience that gives one first-hand impressions not to be gained from investigations of others, about which one can only hear or read.

Functional Activities of the Normal Myocardium

Ventricular muscle has the fundamental attribute of *excitability* by virtue of which minute electrical potentials traveling over muscle systems by a process called conduction, cause every fraction to contract or shorten against the resistance of intraventricular and aortic pressures. In order to contract, each muscle fraction must have an impulse conducted to it and must contain the chemical energy-material (probably adenylpyrophosphate) which on explosion is converted into contractile stress. It is generally believed that this explosion occurs under anaerobic conditions, but that new material is continually reformed during diastole through oxidative processes. In short, we

* Read at the Regional Meeting of the American College of Physicians in Pittsburgh, November 11, 1944.

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may say that release of a "metabolic spring" leads to contraction and the rewinding of the spring takes place during diastole. The chief importance of an adequate flow of blood through the myocardium, therefore, consists in supplying the oxygen for rewinding the machinery and in carrying away the products of combustion. That anoxia, interference with oxidation, and accumulation of waste products with decrease in pH exert deleterious effects on the intact heart, was beautifully demonstrated by Tennant in my laboratory. Tennant [1] exposed and cannulated a branch of the *ramus descendens*

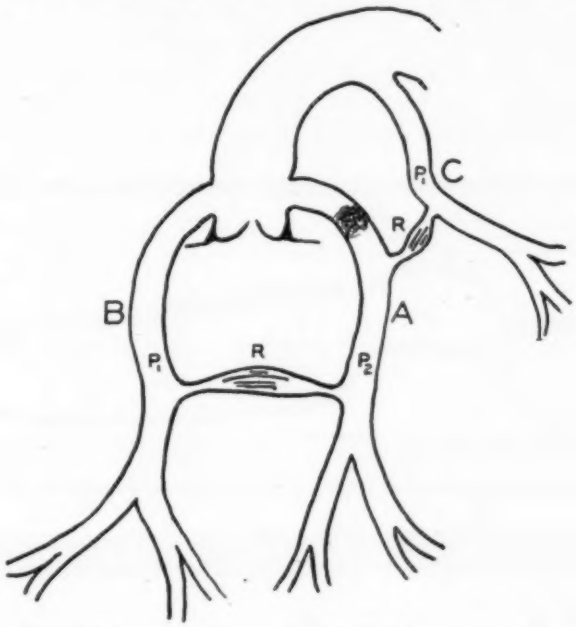


FIG. 1. Scheme showing potential coronary and extracoronary communications that may develop into serviceable channels after occlusion of a major ramus but which are functionally unimportant in normal hearts. Discussion in text.

and connected it to a reservoir of heparinized blood under 100 mm. Hg pressure. By clamping the main branch and allowing such blood to flow through the myocardium, normal contractions continued unabated. But when he added to this blood such agents as KCl (which blocks conduction of impulses), sodium cyanide (which destroys oxidative enzymes) or lactic acid, the region supplied failed to contract. Similar effects occur when the regions are perfused with solutions of reduced hemoglobin or with fully oxygenated Locke's solution which is unable to carry adequate volumes of oxygen for the working heart in the body.

THE EFFECTS OF CORONARY OCCLUSION

In a normal heart, occlusion of any major coronary ramus or its main branches results in an almost immediate failure in oxygen supply, because such anatomical anastomoses as exist are not in fact functional. They are

normally of such small diameters that a sufficient pressure-differential does not exist to irrigate the territory supplied by the main coronary branch. The elementary hemodynamics are elucidated in figure 1. Suppose two adjacent vessels, A and B, supply separate territories of myocardium and that communications (R) exist. Since both of these vessels come from the aorta and since pressures P_1 and P_2 within them are equal, no transfer of blood occurs through the communications regardless of their size. If vessel A be occluded, the volume flow transferred from B to A depends on the pressure difference P_1-P_2, on the square of the cross-sectional area of anastomosing vessels and inversely on the length of the vessels and the viscosity of the blood. Since the last three factors determine impedance to flow they are generally designated as vascular resistance (R). Thus, volume flow $=P_1-P_2/R$. Obviously the same conditions apply to possible extracoronary

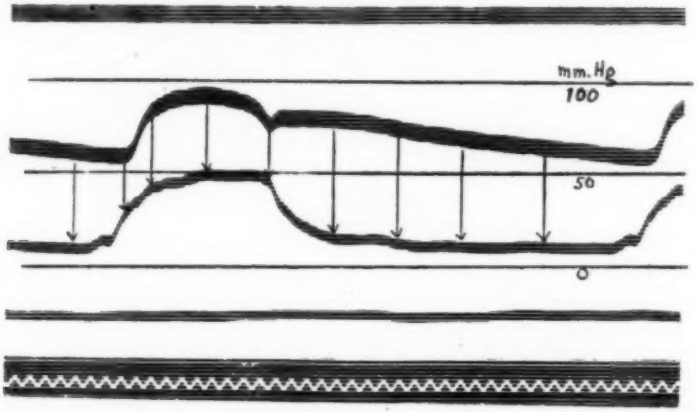


FIG. 2. Optical pressure curves showing range of pressures in an unoccluded (upper) and occluded coronary ramus (lower). Arrows indicate pressure differences at various moments of the cardiac cycle. These are not sufficient to force blood through normal collaterals.

communications represented diagrammatically by vessel C in figure 1. Now, studies of collaterals between coronary vessels (A, B) and between coronary and extracoronary vessels (A, C) by injection methods have shown that the communications are normally sparsely distributed and of small size. When one coronary ramus is clamped and the blood flow from its peripheral end is measured, it generally amounts to only a few drops per minute. Measurements of pressure in an open and an occluded vessel have revealed that the pressure does not approach zero in the latter but rises significantly during systole, owing to compression of intramyocardial branches, thus decreasing the pressure differential materially. Such curves illustrating the effective pressure differences which exist between patent and occluded vessels during the cardiac cycle are shown in figure 2. On the basis of observations such as these, the prediction could be made that the coronary vessels are functional end-arteries. That such collaterals are really inadequate was demonstrated

more crucially in experiments by Tennant and myself [2] by recording contractions from an area supplied by a coronary ramus (e.g., *ramus descendens anterior*) before and after the main coronary was clamped. We found, as illustrated in figure 3, that approximately within 60 seconds the area studied no longer shortened during the period of systolic ejection, but brusquely expanded during isometric contraction under the force of rising ventricular pressure. The stretching of such ischemic areas can also be demonstrated by aid of moving pictures and has in fact been recorded after coronary occlusion in man by the aid of fluoroscopic and roentgenkymographic methods.[3, 4, 5] Indeed, such procedure has been suggested as an additional means for localizing the ischemic area in man and in estimating its extent. Subsequently, H. Green and I,[6] using similar methods, were unable to restore functional contractions in the ischemic area of dog's hearts by use of xanthins, nitrites,

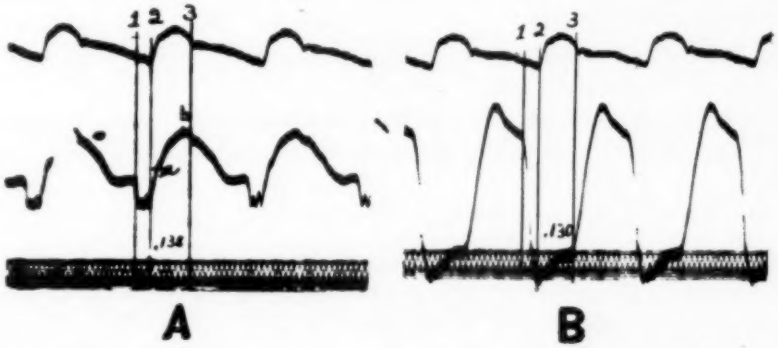


FIG. 3. Aortic pressure curves (upper curve) and myographic records from a region supplied by the ramus descendens anterior (lower curve). A, normal—note that the area shortens during systolic ejection as indicated by upward stroke during interval 2–3. B, 60 seconds after occlusion of the ramus descendens anterior—note that the area expands brusquely during isometric contraction as shown by pronounced downstroke during interval 1–2 and contracts very little during systolic ejection (2–3).

adenylic compounds or epinephrine, indicating that serviceable communications cannot be established in normal hearts by drugs reputed to dilate coronary vessels.

Although collateral circuits are certainly of no importance in furnishing oxygenated blood to a potentially infarcted area in hearts of normal dogs—and quite likely in normal hearts of man—it has also been experimentally demonstrated that they can become serviceable when the main vessel is gradually occluded. The mere demonstration that progressive reduction in the lumen of a main vessel by operative procedures increases the number and size of communications by which one set of arteries can be forcibly injected from another in dead hearts is suggestive, but does not demonstrate that such blood flows through capillaries in the myocardium. The same is true of observations that the pressures and flow in the peripheral end of an occluded vessel augments (Mautz and Gregg [7]). However, the demonstrations by Tennant and Bright in our laboratory that sudden complete occlusion of

the ramus in such hearts is not followed by abolition of contraction in the areas which it supplies is crucial evidence for the adequacy of such newly formed collaterals. It should be added, however, that it has not been demonstrated that development of such efficient collaterals is limited to intercoronary communications; it is highly probable indeed that extracoronary communications (illustrated in figure 1) also develop at the base of the heart. Such development of coronary collaterals through slow narrowing of a main vessel probably explains the occasional necropsy reports of cases in which one ramus had been completely occluded for years without creation of infarcts in the territory which it supplied. Finally, it should be mentioned that it has been demonstrated morphologically that the arterioles, capillaries, sinusoids and venules of the myocardium connect with the ventricular cavities.[8] However, the bulk of experimental evidence strongly suggests that they are not functionally important as collateral supplies when a main coronary is occluded.

The practical conclusion from such experimental observations would seem to be that antecedent gradual narrowing of a main coronary vessel favors the development of collaterals which may be adequate to supply a neighboring territory when sudden complete occlusion of its main branch supervenes.

Dynamic Consequences of Abolition of Contraction in Ischemic Areas

Although a search of the literature reveals that experimenters previous to Tennant and myself had noticed—or believed they had observed—an absence of contraction or bulging of an ischemic region, it is certain that its significance for the dynamics of the heart beat and circulation were not appreciated by them. However, Orias[9] reporting from my laboratory in 1932 had actually predicted that changes in the form, amplitude and duration of ventricular pressure curves and the consequent changes in the dynamics of the whole circulation must be initiated by just such absence of contraction in an ischemic area. His analysis and all subsequent studies lead clearly to the conclusion that the cardiac and circulatory embarrassment which follows coronary occlusion in man is also initiated by such deletion of contracting muscle blocks. This not only reduces the total myocardial force available for raising intraventricular tension but some of this pressure is spent in stretching the ischemic area and is thus lost for expelling blood into the aorta. The immediate consequences are shown in records A and B of figure 4. The ventricular pressure maximum is lowered, systolic discharge is reduced, pulse pressure in the aorta is decreased, and systolic and diastolic pressures fall. In addition, the period during which blood is expelled is reduced from .134 to .121 second, as a result of the deletion of contracting myocardial fractions. However, as shown in curve C of the same figure, taken four minutes later, the heart has compensatory mechanisms by means of which dynamic conditions can be restored to normal, provided the remain-

ing myocardium is in good responsive condition. I may add parenthetically that while this accords with general clinical belief, the experiments just quoted are to my knowledge the only ones on record which demonstrate that compensation occurs not through improvement of circulation in the affected area but through enhanced action of the myocardium which is not involved. Experiments such as these do still more; they suggest the mechanism by virtue of which the rest of the muscle responds promptly to the needs.

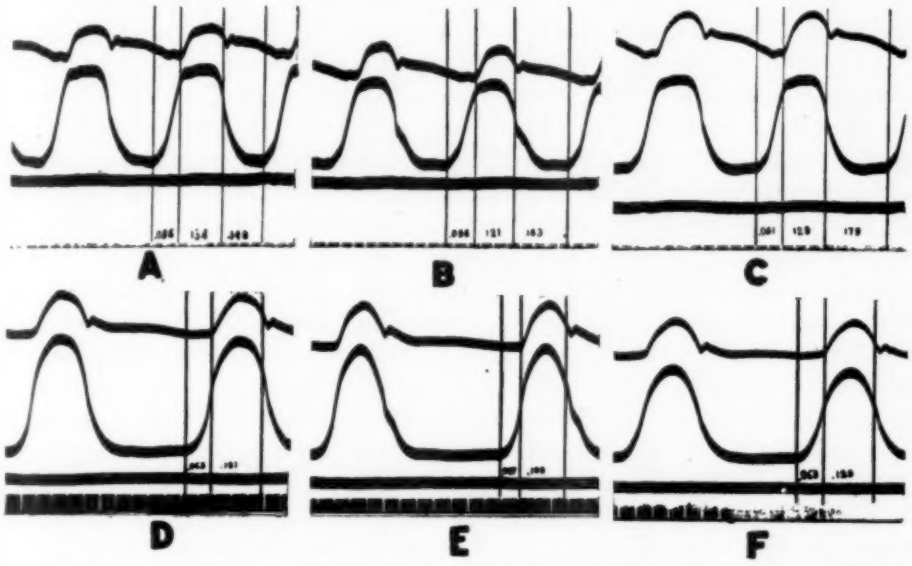


FIG. 4. Aortic pressures (upper curves) and left ventricular pressures (lower curves). A, control. B, shortly after occlusion of ramus descendens anterior. C, after development of compensation. D, control from another animal. E, shortly after occlusion. F, later, with failure of compensation. Discussion in text.

For details, other sources must be consulted.[10] Briefly, the following series of events is involved: During hypodynamic beats (curve B) the ventricles expel less blood; the accumulating systolic remainders added to oncoming blood raise diastolic pressure in the ventricles and stretch the viable muscle; this muscle, in accordance with the law of initial tension and length—sometimes called Starling's law—contracts more vigorously, thereby restoring cardiac output and arterial pressures to normal. However, not all dogs under anesthesia and submitted to operative procedures necessary for exposing the heart react as well, because the viable portion of the myocardium may not respond to stretch. In that event, as shown by curves D, E, F of figure 4, obtained from another dog, ventricular pressures reach the lower maxima, the pulse pressure decreases and arterial pressure falls progressively. The ventricles, atria, pulmonary vessels and veins fill with blood; in short, "back-pressure effects" become operative.

Circulatory Failure, Shock and Collapse

Although it is clear from experimental studies that myocardial failure is the crux of the circulatory failure which follows, secondary reactions take place which change the picture both in dogs and in man in such a way that dynamically and symptomatically it is often difficult to separate from that of experimental or clinical shock due to loss of blood or plasma. When this occurs the clinician is apt to declare that a state of circulatory failure, shock or collapse exists. Is such terminology warranted? The answer depends on whether we choose to make the diagnosis of "shock" on the basis of clinical signs and symptoms or on the basis of which part of the cardiovascular system is primarily affected and ultimately defaults. The similarity of clinical syndromes following coronary occlusion and loss of blood or plasma is due to the fact that, in both cases, cardiac output is decreased, but for different reasons. The same compensatory mechanisms are, therefore, set in operation regardless of whether reduced systolic discharge is primarily due to defective return of blood, as in hemorrhage, to hindrance of ventricular filling, as in pericardial effusions, or to depression of the total contractile capacity of the ventricles, as in uncompensated cases of acute coronary occlusion. One of the consequences of lowering arterial pressures is that moderator vascular reflexes operate to cause generalized vasoconstriction,—in the viscera as well as in the muscles and skin. Now it seems probable as a result of recent studies that visceral constriction acts dominantly to increase total peripheral resistance, thus helping to sustain arterial pressure, but that constriction of skin vessels acts chiefly by diverting blood from the capacious skin reservoir to internal organs. In circulatory failure due to loss of blood or plasma this transfer of blood acts in a compensatory manner by increasing the volume of blood returned to the heart with the result that cardiac output and arterial pressures are raised. In coronary occlusion it merely tends to intensify the engorgement and adds to the volume of blood that the defective myocardium cannot move. Moreover, cutaneous constriction is intensified by reflexes associated with the intense pain and so helps to create a surface appearance which cannot be distinguished from that of shock due to peripheral circulatory failure. In addition, the pulmonary congestion induces respiratory reflexes which lead to hyperpnea or dyspnea of a grade rarely seen in shock. Since venous flow is retarded, cyanosis is generally more intense than in shock due to loss of blood or plasma, but this difference may not be conspicuous.

It is obvious that if clinicians insist in making the diagnosis of shock on the basis of low blood pressure, small pulse, feeble rapid heart action, clammy, cold, pale or cyanotic skin, drawn expressions, etc., without regard to the initiating mechanism and mode of terminus, the circulatory failure following coronary occlusion comes in the category of clinical shock. Scientifically, however, the circulatory failure of coronary occlusion does not belong to the category of shock, for unlike conditions to which this term is re-

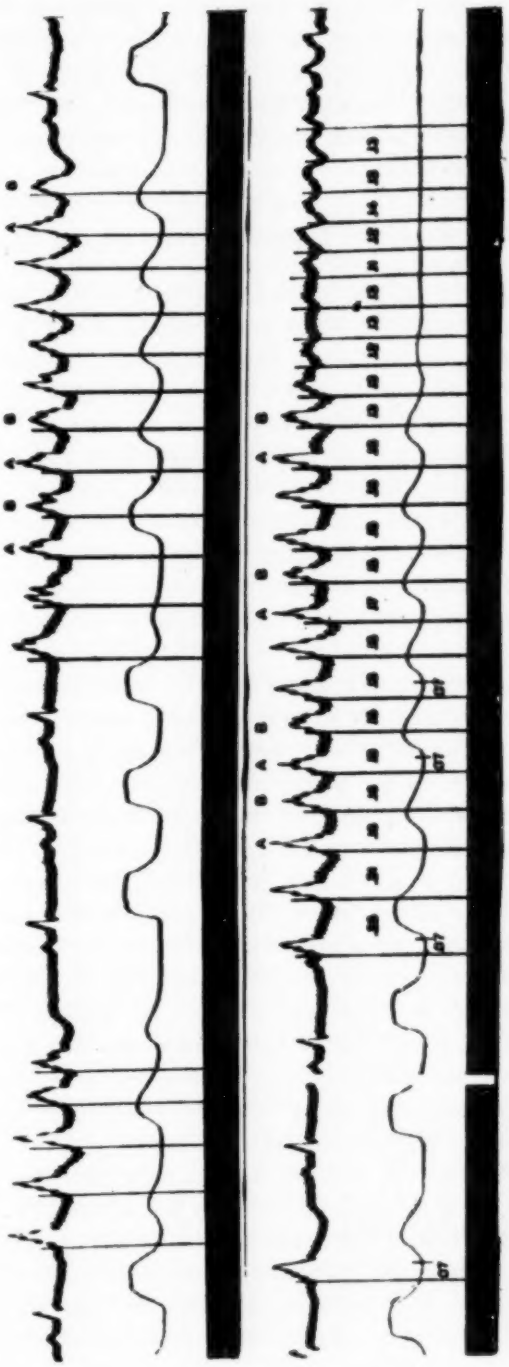


FIG. 5. Electrocardiograms, Lead II (upper records) and left ventricular pressure curves (lower records) from two animals showing development of short tachysystolic periods and the development of ventricular fibrillation in the lower set of records. Discussion in text.

stricted by common consent it is not initiated by reduction in effective circulating volume and venous return and death does not ordinarily occur as a result of an irreversible state in the peripheral vessels. For therapeutic reasons, if for no other, the conditions should be differentiated in our terminologies; in one, transfusions improve the circulation, in the other they would only embarrass the heart.

Cardiac Irregularities

As soon as an area of myocardium becomes ischemic, spontaneous foci tend to develop from which impulses are discharged. These give rise to premature contractions or transient periods of ventricular tachycardia. When the impulses are not emitted in regular sequence but in an accelerating manner, fatal ventricular fibrillation eventuates. Although the development of such arrhythmias has long been known to clinicians and experimentalists alike, the conditions which favor or induce them remain obscure. My associates and I have, for several years, studied the physiological condition of the ischemic muscle from various angles, and while many interesting facts regarding its state of excitability, conductivity, polarization and feeble efforts at contractions have been established, the fundamental explanation for the development of rhythmic or sporadic foci is still undecided.[11, 12]

The occurrence of cardiac irregularities or tachycardia is detrimental for maintaining a balance of the circulation even under normal conditions of the circulation. However, owing to the operation of various compensatory mechanisms, they rarely prove significant. When, however, after coronary occlusion, these compensatory mechanisms are already utilized and particularly when the maintenance of a good circulatory balance is being barely accomplished, the supervention of irregularities may cause serious cardiac decompensation. They intensify "back pressure effects," reduce cardiac output, and lower arterial pressure. Furthermore, not every ectopic excitation which develops and is recorded in electrocardiograms elicits a mechanical systole. This is illustrated in the two records of figure 5. In the upper set of records, the standard Lead II reveals two groups of excitations constituting short tachysystolic paroxysms. The ventricular pressure curve shows only half the number of mechanical systoles, generally of reduced size. Obviously alternate excitation waves (B) released in the ischemic area are ineffective, because they arrive during the refractory periods of the functioning muscle. The lower set of records shows a somewhat longer series of similar excitations which are alternately effective (A) and ineffective (B) and, as the frequency increases the ventricles fibrillate. The danger always exists that such accelerating rhythms leading to fibrillation may develop at any time. The onset of such fibrillation is the only reasonable explanation for sudden death, either at the onset or during the course of coronary occlusion.

Ventricular fibrillation is an "incoördinate" type of contraction which produces no effective beats. As a result, arterial pressure falls abruptly to very low levels and death from cerebral anemia supervenes. For a number of years, various members of my staff and I have been interested in studying the mechanisms of fibrillation and its mode of onset. The bulk of experimental evidence indicates that fibrillation once developed represents a condition in which an incoördinated reëntry of impulses occurs because blocks occur in various regions and impulses are forced to zigzag their way through cardiac tissue. While some of them return ultimately to some part of the original path, the locus of reëntry is not definite, as Lewis believed to be the case in atrial fibrillation. As to the mode of onset, we are convinced that the stage of fibrillation is immediately preceded by a series of tachysystolic discharges from some single focus. When, as shown in figure 5 (lower set records), their frequency increases beyond a critical level, blocks develop which prevent an orderly excitation of viable myocardium. Consequently some impulses reënter and the ventricles fibrillate.

The question still remains as to the cause of these repetitive focal discharges and the conditions which give rise to them. As regards the latter, we have explained and obtained evidence for each of two possibilities. Wegria, Pinera and Wiggers [11] obtained evidence that the fibrillation threshold in the ischemic area is decreased to such an extent that a chance premature natural impulse arising during the late moments of systole may give rise to a repetitive series of discharges. Harris and Guevara Rojas [12] favor the view that electrotonic currents develop across the margins of an ischemic area which, as in nerve cells and fibers, develop a rapid repetitive accelerating rhythm.

Cardiac Pain

Cardiac pain and its concomitants are probably the most outstanding features of coronary occlusion, although many cases have been reported in which significant pain appears to have been absent. Experimental studies have demonstrated that the impulses giving rise to sensations of pain travel over the sympathetic system. Their pathways are probably as follows: (*a*) *via* left middle cardiac nerves to the middle cervical ganglion, through the cervical cord and stellate ganglion, entering the cord by white rami of the first to the fourth or fifth thoracic ganglia, (*b*) *via* left inferior cardiac nerves to the stellate ganglion, and thence, as above, (*c*) *via* numerous direct connections between the heart and left upper five or six thoracic nerve roots.

The intense agonizing pain is made more unbearable by the development of disagreeable reflex actions. Segmental visceromotor reflexes increase the tonus of thoracic muscles which is appreciated in consciousness as an unpleasant sense of thoracic constriction. Reflexes to the stomach and gut cause reduction in tonus, and the drag thereby created causes a sinking feeling in the epigastrium. Nausea and vomiting often occur. The reflexes which, as in renal and biliary colic, cause pallor and coldness of the skin have

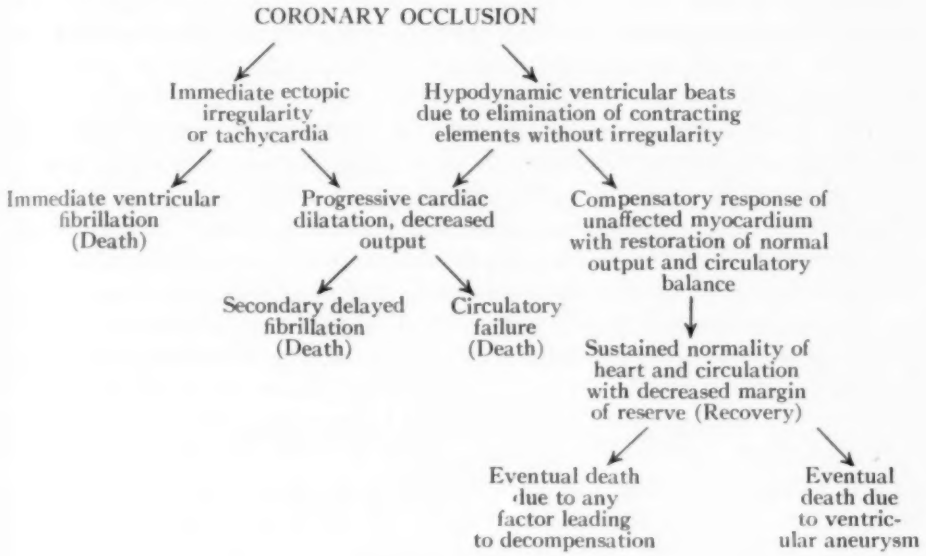
already been mentioned. These and other concomitants of pain create a feeling of impending dissolution and in some instances may even eclipse the pain itself.

The mechanisms by which pain endings are stimulated in the heart have been investigated repeatedly. The bulk of experimental and clinical investigation favors an origin within the ischemic area, but whether terminals are distributed throughout the muscle or are limited to connective tissue sheaths of blood vessels remains undecided. The preponderance of evidence also indicates that chemical agents formed as a result of anaerobic metabolism act as stimuli, but their identity has not been discovered. To call them P-substances, as Lewis has done, does not advance our knowledge. Uncertainty also exists as to whether chemical substances accumulate to threshold values because oxygen is lacking, or merely because they cannot be washed away. Finally, the possibility exists that mechanical stimulation may play a part. It has been suggested that this could occur as a result of (1) an extreme distention of arteries proximal to a thrombus by high aortic pressure, (2) compression of sensory endings by contraction of vascular branches distal to occlusion, or (3) periodic stretching of the ischemic area. I have found that similar periodic stretching of a skeletal muscle such as the gastrocnemius, evokes reactions which are unquestionably associated with pain. The fact that the pains are not rhythmic with the heart beat does not discount such a possible origin for, in the conduction of impulses enunciating pain, central summations of impulses occur which prevent the brain from appreciating their rhythmic character. Such an hypothesis would more easily account for the amelioration of pain by reduction of arterial blood pressure, for it could not affect the chemical agents within an ischemic region, but could cause less stretching of the walls in the affected area.

Summary

The myocardial effects of coronary occlusion are the immediate result of ischemia which may be defined physiologically as anoxia plus accumulation of products of anaerobic metabolism. This induces two dangerous conditions: It creates a functional state at or near the borders of the ischemic zones which favors production of ectopic beats which may lead to ventricular fibrillation and it eliminates contractile functions of the affected muscle, thereby throwing the burden of work in maintaining an adequate cardiac output on the remaining muscle. If this muscle is able to respond in accordance with physiological rules, compensation occurs. If it does not or fails to maintain compensation, acute or progressive cardiac failure results which may lead to clinical symptoms and signs distinguished with difficulty from "shock" or circulatory failure of peripheral origin, but which are not due to such failure. The anoxia or chemical products of metabolism or both and possibly the mechanical stretching of the ischemic area excite pain endings and usually cause the suffering associated with coronary occlusion.

The sequential changes which early or late may lead to a fatal outcome are schematized in the following chart [13]:



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LYMPHOCYTOSIS IN THE CEREBROSPINAL FLUID*

By Irving L. Applebaum, Lt. Col., M.C., F.A.C.P., Joel Shrager, Major, M.C., and William Paff, Major, M.C.

The increase of cells in the cerebrospinal fluid may be either in the number of mononuclear lymphocytes or polymorphonuclear leukocytes and is invariably an indication of a pathological process. The predominant finding of polymorphonuclear elements points to a suppurative lesion and the scope of differential diagnosis is relatively limited. However, lymphocytosis presents a wider range of diagnosis, treatment and prognosis.

During an 18 month period (1942–1943) there were 72 cases of lymphocytosis in the cerebrospinal fluid caused by a variety of etiological agents.

Table I

Causes of Lymphocytosis in Cerebrospinal Fluid

(72 Cases)

Diagnosis	No. Cases	Per. (%)
1. Mumps meningo-encephalitis	30	41.6
2. Acute lymphocytic meningitis, benign (cause undetermined)	17	23.6
3. Syphilis of central nervous system	7	9.7
4. Tuberculous meningitis	4	5.6
5. Chemical meningitis (intrathecal serum, etc.)	3	4.2
6. Acute encephalitis, cause undetermined	2	2.8
7. Tetanus	2	2.8
8. Trauma of brain	1	1.4
9. Abscess of brain	1	1.4
10. Cysticercosis of C.N.S.	1	1.4
11. Rabies	1	1.4
12. Lymphocytic meningitis associated with malaria	1	1.4
13. Guillan-Barre syndrome	1	1.4
14. Infectious mononucleosis	1	1.4

Table 1 is a résumé of the number and types of factors. The two most commonly encountered diseases were mumps meningo-encephalitis (41.6 per cent) and acute benign lymphocytic meningitis, cause undetermined (23.6 per cent).

Clinical Aspects of Mumps Meningo-Encephalitis. Of 945 cases of epidemic mumps there were 30 (3.2 per cent) complicated by meningo-encephalitis with a lymphocytic reaction in the spinal fluid. Nine (30 per cent) of these 30 cases exhibited evidence of orchitis and three (10 per cent) suffered from pancreatitis, suggesting the widespread systemic invasion by the virus of mumps with a predilection for certain systems.

The onset was usually acute and occurred about 4.5 (average) days after the first signs of parotitis. On two occasions meningitic signs appeared a

* Received for publication October 4, 1944.

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few days prior to evidence of salivary gland involvement and in one case central nervous system signs were elicited 12 days after the onset of parotitis. The more severe cases seemed to occur early in the course of mumps. Frontal headache was the most common complaint and then there followed in order of frequency increase in feverishness, vomiting, nausea, dizziness and nervous irritability. One patient had mild convulsions, which subsided after 24 hours.

An exacerbation of temperature occurred in all cases and averaged 3.5 days in duration. Except for nuchal rigidity, which was detected in 20 cases (66.6 per cent), there was a paucity of the classical signs of meningitis. Hyperactive reflexes were recorded in five cases, Kernig's sign was elicited in two cases, abnormal pupillary reflexes in two and Brudzinski's sign in one. These objective findings were transient and disappeared within 48 to 72 hours. There were no complications or deaths.

The average cell count of the spinal fluid was 298 per cubic millimeter (80 to 100 per cent lymphocytes) during the peak of the illness. The highest count was 1,298 cells and the lowest was 39 cells. Moderately increased pressure of the spinal fluid was noted in the majority of cases. Other studies of the spinal fluid, including the Wassermann reaction, the colloidal gold curve, glucose content and bacteriological culture, were normal. Several instances of increased protein were recorded. Serial cell studies, performed in many cases, revealed that in general the cell count reached its highest level in two to three days and then gradually tapered off, so that at the end of approximately 10 days the spinal fluid was cytologically normal. The clinical picture, subjective and objective, cleared within a few days and did not run parallel with the lag in pleocytosis. Other laboratory data were unimportant. Figure 1 represents a composite picture of the clinical course of mumps complicated by meningo-encephalitis.

Clinical Aspects of Acute Benign Lymphocytic Meningitis. This group includes all cases of lymphocytosis in the cerebrospinal fluid in which no specific etiology could be ascertained and the clinical course resembled cases described in the past as acute benign lymphocytic meningitis or by other synonyms. Patients were mainly young adult males of varied racial groups.

The prodromal period lasted approximately four to five days prior to meningeal signs and was manifested by respiratory, gastrointestinal or systemic symptoms. The chief complaints on admission to the hospital were headache and nuchal rigidity. Less common symptoms listed in order of frequency were vertigo, feverishness, photophobia, anorexia, lethargy and mild convulsive movements. The objective signs were nuchal rigidity (88 per cent), Kernig's sign (70 per cent), abnormal reflexes (65 per cent), Brudzinski's sign (17 per cent). There was only one case without any objective signs and his only complaints were frontal headache and slight feverishness.

The cytological study of the cerebrospinal fluid, performed within 48 hours of admission, revealed an average of 322 cells per cubic millimeter.

The lowest was 54 cells and the highest was 950 cells. Ninety to 100 per cent of all cells were lymphocytes. Upon serial studies of spinal fluid cytology it was noted that, in general, the count reached its peak within several days and gradually subsided, so that it was within normal limits in three weeks. As in mumps meningitis the clinical picture cleared rather early (usually within one week) and there was a lag in the cytological picture. Except for a proportionate increase in pressure and protein content (50 to 90 mg. per 100 c.c.), all other studies such as the Wassermann reaction, the colloidal gold curve, bacteriological culture, glucose and chloride contents, were normal.

Clinical Pattern of Mumps Meningo-Encephalitis

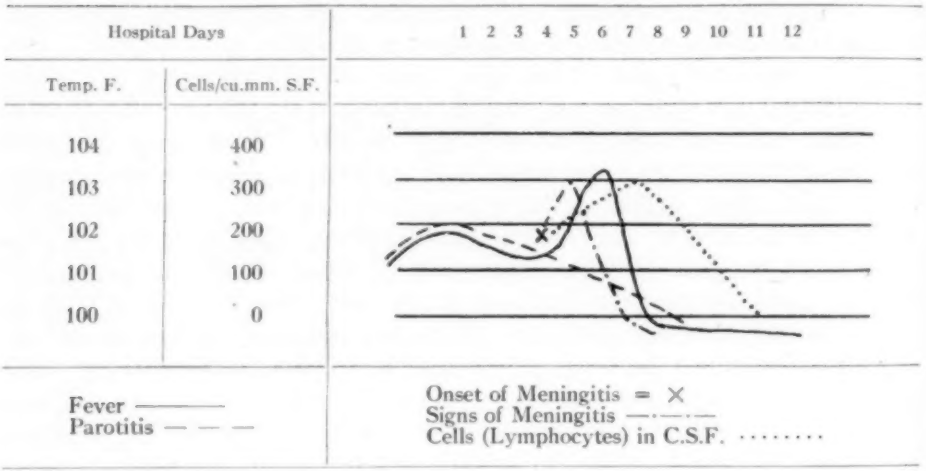

FIG. 1

Ten cases were subjected to chemotherapy in the form of sulfa drugs (sulfadiazine) and seven received only palliative treatment. All ran a self-limited course and there was no appreciable difference between the sulfa-treated and non-treated groups. Patients were usually well within 10 days and the average hospital stay was one month. One case was complicated by left facial paralysis. Neither relapses nor deaths occurred in this series. Figure 2 represents a composite picture of the clinical course.

Miscellaneous Conditions. There were seven cases of syphilis of the central nervous system with lymphocytosis in the cerebrospinal fluid. The average cell count was over 200 per cubic millimeter and the total protein was proportionately increased. Five were diagnosed as meningovascular syphilis, one as general paresis, and one was unclassified. Positive serologic reactions (Wassermann) of the blood and spinal fluid were reported in all. The colloidal gold curve revealed a mild mid-zone rise except in the case of general paresis, in which an initial elevation was observed. It was interesting to note that in three cases there was no history of a primary infection

and, therefore, no therapy had been instituted. In the other four cases, although the primary lesion antedated the discovery of the central nervous system lesion by three to eight years, the course of treatment on the basis of history was considered inadequate in all but one.

There were four cases of tuberculous meningitis: three in children as part of a generalized miliary tuberculosis and one in an adult as the terminal event of advanced bilateral pulmonary tuberculosis. The average cell count of the initial spinal fluid study was 189 per cubic millimeter, the protein was elevated, and glucose was slightly diminished. In two cases the initial study

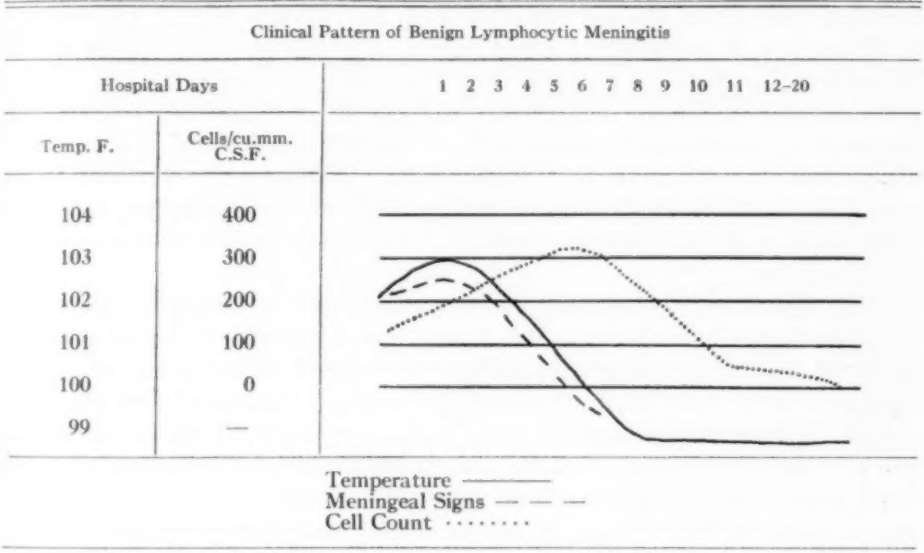

FIG. 2

revealed a moderate polymorphonuclear response, but in subsequent tests there was a preponderance of lymphocytes. In two of the four cases pellicle formation and the presence of acid-fast bacilli were detected. The mortality rate was 100 per cent.

In the group of three cases due to chemical irritation, the cell count was moderate and transient. The following factors were responsible: (1) Antimeningococcus serum employed intraspinally in meningococcus meningitis. (2) Tetanus antitoxin administered intrathecally in tetanus. (3) Novocaine solution injected intraspinally for anesthetic purposes.

In the remainder of the cases, the clinical history and course, and the laboratory data aided in the solution of a specific diagnosis. Two cases fitted the pattern of acute encephalitis (virus). Two proved cases of tetanus and one case of rabies, confirmed by postmortem examination, produced a spinal fluid lymphocytosis. Trauma (1 case) and abscess of the brain (1 case) also induced sterile lymphocytic reactions (meningitis sympathica). One case was due to the Guillan-Barre syndrome (albumino-

cytological dissociation and peripheral neuritis), one was associated with severe aestivo-autumnal malaria and considered of undetermined etiology, one was part of the picture of acute infectious mononucleosis and in one case a tentative diagnosis of cerebrospinal cysticercosis [1] was made.

Comment

The incidence of mumps meningo-encephalitis in this series (3.2 per cent) is lower than expected. However, if routine lumbar punctures were performed in all cases, the rate undoubtedly would be increased. Reports in the literature vary from 0.1 per cent, based on postmortem studies by Larkin,[2] to 40 per cent in cases where spinal taps were performed by Finklestein [3] in 40 consecutive cases of mumps. Between these two extremes the figures were variable and were undoubtedly influenced by diagnostic acumen, the frequency of lumbar punctures, and the virulence of epidemics. Occasionally clinical evidence of parotid or submaxillary glandular involvement is so scanty as to make an etiological background difficult to establish. As a matter of fact, primary mumps meningitis without glandular involvement has been described.[4, 5, 6, 7]

The neurological syndrome, which seems to follow a classical pattern in the majority of cases, is caused by the virus of mumps. Because of the rarity of deaths, pathological descriptions of tissue are uncommon. Postmortem reports have been submitted by Larkin,[2] Donahue,[8] Urechia [9] and others. Edema of the surface of the brain, congestion of the pia-arachnoid and perivascular infiltration of the pia-arachnoid and the cortex by large and small mononuclear cells have been reported. Gordon [10] performed experimental work in 10 monkeys by means of the intracerebral injection of the virus of mumps, obtained by the passage of a gargle specimen from an uncomplicated case of mumps through a Berkefeld filter. Four animals exhibited central nervous system symptoms and died within several days. He noted lymphocytosis in the cerebrospinal fluid, degenerative changes in the nerve cells and perivascular and cortical infiltration.

Brenneman [11] divides the neurological syndrome of mumps into meningitic and encephalitic forms. The latter have cell counts of about 200–300 per cubic millimeter of spinal fluid and a paucity of objective signs. The former have higher cell counts and signs indicative of meningeal irritation. It is universally recognized that the prognosis is excellent and complications are infrequent. Although there were none in this group, such residuals as permanent deafness, blindness, spastic paralysis and idiocy have been listed.

In the majority of cases of cerebrospinal fluid lymphocytosis of undetermined origin, the clinical picture closely resembled that of acute lymphocytic choriomeningitis due to a virus first defined by Armstrong and Lillie [12] in 1934 or a condition due to an allied virus such as one isolated by McCallum, Findlay and Scott [13] in 1939. No facilities for identification of viruses were available to us. However, even where such facilities are present, identifica-

tion is not always possible. For example, Baird and Rivers [14] in 1938 were able to isolate the specific filterable virus in only 28 per cent of their clinical cases. Of interest in this zone, where both mice and mosquitoes are plentiful, are the reports of Coggeshal,[15] who transmitted the virus of lymphocytic choriomeningitis to a guinea pig by means of the bite of an *Aedes aegypti* mosquito, and of Armstrong,[16] who has demonstrated that mice are important vectors in transmission of the disease to man.

In about one-third (six cases) of our series the disease resembled aseptic meningitis described by Wallgren.[17] In this group the prodromal period was shorter, the disease was more benign, the cell count was lower, no residuals occurred and convalescence was more rapid.

As a clinical aid in the differential diagnosis of cases with lymphocytosis in the cerebrospinal fluid, the following classification is submitted:

1. *Acute lymphocytic meningitis (benign):*
   a. Acute lymphocytic choriomeningitis.
   b. Lymphocytic meningitis due to allied viruses.
   c. Aseptic meningitis, cause undetermined (Wallgren).
2. *Other diseases of virus origin:*
   Mumps, acute encephalitis (varieties), poliomyelitis, rabies, herpes (zoster and simplex), the common contagions, post-vaccination, lymphogranuloma venereum, infectious mononucleosis, Guillan-Barre syndrome, etc.
3. *Specific bacteria:*
   Tuberculosis, syphilis, tetanus.
4. *Fungi and parasites (uncommon):*
   Torula infection, cysticercosis, etc.
5. *Chemical factors* (intraspinal injections):
   Serum, novocaine solution, lipiodol, etc.
6. *Meningitis sympathica* (irritative):
   Sequela to trauma of brain, aural infection, subdural abscess, epidural abscess.

Summary

1. A group of 72 cases, presenting evidence of lymphocytosis in the cerebrospinal fluid, was studied at Gorgas Hospital (Canal Zone) during an 18 month period.

2. A variety of etiological factors was detected. The two most common diseases in this series were mumps meningo-encephalitis (41.6 per cent) and acute benign lymphocytic meningitis (23.6 per cent). Syphilis, tuberculosis, chemical irritation (intrathecal injection) and other causative agents were listed.

3. The clinical patterns of mumps meningo-encephalitis and acute benign lymphocytic meningitis were presented in detail, and the early clearance of the clinical syndrome with a relative lag in spinal fluid pleocytosis was a prominent feature of both diseases.

4. A clinical classification was submitted as an aid in the differential diagnosis of lymphocytosis in cerebrospinal fluid.

Acknowledgment is given to Capt. Bliss C. Shrapnel, M.C., who assisted in the clinical studies of these cases. Gratitude is expressed to Ann Crecelius, section secretary of Gorgas Hospital, for her aid in preparation of this manuscript.

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NEUROSES IN THE COMBAT ZONE*

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Little did any of us believe, four years ago, that our nation, morally decent and peaceloving, could be developed into the greatest military power in the history of mankind! Little did we realize that we could mobilize our manpower and production to provide the necessary material to prosecute this global war. We not only succeeded in preventing enemy invasion of our own shores but helped turn the tide for our beleaguered allies who were facing impending disaster. A few years ago we were a smugly complacent pacifistic democracy, comfortably entrenched in a false feeling of security due to what we thought was geographical isolation. Today, the problems of the world are *our* problems and we have succeeded in making the necessary emotional and mental adjustments to include the problems of the downtrodden and lesser world powers with our own. In part, our interest has expanded because today we find American youth fighting shoulder to shoulder with the people of almost every land in all corners of the globe, and we are helping them in material ways to rid the world of the evil forces which would have destroyed our civilization. Even though we cannot share the ardent hatred with those countries who have been ravished by a designing and cruel foe, we can say that America has developed a potent philosophy—our Good Neighbor policy—which has carried us so far toward the victorious termination of this great world conflict. We must admit that both our soldiers and our people lack that passionate hatred for our enemy because we have not experienced, as a nation, the deep-seated bitterness and resentment toward a ruthless enemy who has wantonly destroyed the civilian population and homes of our allies. Pearl Harbor and reported Jap and Nazi atrocities kindle such a flame, we respond temporarily in an emotional way, but the flame dies down because our American homes are intact and our families safe from enemy assault and the war is reaching a successful conclusion. To preserve the emotional armament necessary to win an early peace we must stimulate a political, moral and religious fervor—a high morale. The rôle of a high morale will be discussed at greater length.

Medicine has shared very materially in the success of our tremendous effort. We contributed our part, both in the selection of the manpower fit to fight, and in the care of those who became casualties. The appalling statistics of physical and mental unfitness, revealed by our Selective Service induction examinations, startled the nation, but not the profession. With a reasonably careful screen the great proportion of the physically and mentally unfit were rejected. During the ensuing months our men passed

* Presented at the Regional Meeting of the American College of Physicians, November 4, 1944.

through reception and training centers and were assigned to units for further training, where many more men were found unequipped for service and were discharged. In spite of these repeated screens and surveys, however, many thousands of men who were poorly equipped for combat overseas, escaped detection. The omissions and imperfections of our methods of examination are partly to blame for this additional burden on the Medical Department. Further difficulty results from our inability properly to evaluate all of the factors that make up the highly complex human mechanism. We still know of no yardstick of measurement that will foretell the reaction of any individual under the abnormal stress and strain of war. The experiences gained in World War I and during the 20 years that followed have added greatly to our knowledge and understanding of the human mechanism, but we are still far removed from that complete understanding and appreciation of the intricacies and vagaries of human behavior.

We recognize, therefore, that many individuals reach the combat zone who are basically poorly equipped and in whom antecedent neurotic maladaptation is latent. Those, with similar predisposition, who developed disabling neuroses when first exposed to military life or during the early training period in the states, should be considered as suffering from a relatively severe neuropathic disturbance. In these people the environment and stress are little more severe than those experienced in civilian life. They are of little military value and early separation from the service may permit of a reasonable adjustment at a former civilian level. Those who develop "gangplank fever" or who break beyond the three mile zone or survive the ocean voyage only to "crack up" after landing on friendly foreign shores still belong to the same group in whom preëxisting psychological traumata are inherent and determining factors. The clinical pictures, prognosis and treatment are almost identical with those observed in civilian practice. Experience has proved that attempted rehabilitation of these individuals, with the hope of restoration to a duty status with troops, is futile.

Moving forward toward the combat area we find still another group that develops anxiety states provoked in a great measure by wild stories and exaggerated rumors of fellow soldiers. This, together with a tension state and associated loss of sleep, is sufficient to produce a mental upheaval. These cases undoubtedly have scars of former mental disruptions, but we found they could be made to live with their neurosis if assigned to units in the rear and they were not lost to the army.

Our next group of mental casualties occurs in the area immediately behind combat activity. It is reasonable to assume that any soldier who has succeeded in masking his neurotic pattern up to actual entrance into combat is not suffering from a malignant disorder.

At this point we shall consider the many provocative factors that are a part of the overall picture, influencing the lives of even the normal individuals who find themselves in this abnormal setting. Having served on only one

active front I choose to describe the tangible factors that were evident in our theatre, namely, the S.W.P.A.

Ernie Pyle, Major Ralph Ingersoll, Captain Spiegel, Captain Appel, Lieutenant Colonel Grinker, Commander Braceland, Colonel Porter and many others have masterfully portrayed the picture as they saw it in the African, Italian and European theatres. Their reports should be read to provide the background for better understanding of the problem and the reaction of our soldiers in combat.

In tropical warfare we found environmental factors that are not obvious in other theatres of war. It is felt that they add materially to the development of neuroses among our troops. The heat of these islands, although high, is not unbearable. The humidity, approaching saturation for months on end, is devastating. A noticeable weight loss is evident after a few months in the tropics. Nearly every soldier loses an average of 10 per cent of his normal body weight. This is not due altogether to poor food or food deficiencies. Initially, all troops practice rigid salt discipline. As the months roll by one becomes accustomed to excessive sweating and a proper salt balance is almost universally neglected. A chronic low blood chloride level may account for what has been described as a tropical neurasthenia. It is firmly believed that a marked weight loss with concomitant reduction in general physical stamina is a predisposing cause for many neurasthenic complaints. Frequently a mild gastrointestinal upset with diarrhea may be the forerunner of an acute mental break. One point universally agreed upon by all who spent a year or more on the tropical islands was that a chronic state of fatigue developed in direct proportion to the duration of service of troops in these areas.

Extended effort for a short time during actual combat brings about exhaustion and favors the development of neuroses of combat origin. We who served there knew of many normal men who finally reached their elastic limit, both mentally and physically, and cracked under the strain. This opinion is shared by all medical officers and psychiatrists who served with combat troops.

I dare say that if we were all to be carefully psychoanalyzed, previous neuropathic traumata might be uncovered in all normal people. To conclude that these early experiences finally come to the fore and play an active part in crushing the ego strength and defense is obviously absurd! We know that the fatigue and exhaustion and the stark realism and gruesome wanton destruction, which surround the fighting man, will cause a gradual collapse and regression of the normal ego.

The tropical islands present other problems. There are no safe rear areas for rest or refuge. Earlier in the war when the Jap had air superiority and control of the sea lanes, bombing, strafing and naval guns added to the discomfort and anxiety of combatant as well as noncombatant troops alike. There was no escape. The repeated mental insult of constant shelling finally dulls the normal sensorium, and men became automatons. There is a sense

of unreality about these attacks. Many admit of retrograde amnesia as though there were a mild concussion following the explosion of bombs and heavy shells. This was more common among the men who were unable to retaliate against the enemy attack. The men who manned the antiaircraft guns, the machine gunner, and even the rifle man, suffered less in these attacks. They could release and expend the pent-up emotions and burn up, through activity, the glycogen mobilized by excessive adrenal activity. They were less tense when it was over. By comparison, the unarmed inactive soldier who sought shelter in a foxhole or slit trench showed a greater pallor and less facial expression, a greater paucity of free associated movement, some tremor and all the signs of excessive adrenalinization, and a thalamic syndrome. It took him longer to regain his normal poise. After the attack there was a compensatory hyperactivity and loquaciousness sometimes bordering on an hysterical outburst of yelling and swearing when the "all clear" signal was given. It should be obvious that daily repetition of such assault and mental insult would undermine even the most stalwart unemotional type. It became the duty of every company officer to observe the after effect of these attacks upon the members of his command. Two observations were significant. Increased hyperactivity and overacting, with almost a false bravado, although compensatory, was watched with suspicion. Some of these men became aggressive and manic-like with subsequent similar experiences. The soldier who became irritable, depressed and seclusive, and who failed to carry out or to obey orders for the first time, and who was known to go without sleep, was sent to the medical officer for advice and medication. Rationalization of his fear, reassurance, and a mild hypnotic most often brought about a rapid restoration. He was watched very carefully during subsequent enemy attacks and if he demonstrated further regression he was hospitalized. It was rare to find men who succumbed to single enemy assaults. Repeated exposures in a trying physical environment in people who were exhausted from physical hardship, or convalescent from physical illness, produced ego regression and disintegration. The rôle of the combat team psychiatrist in evaluating the condition of the troops and counciling with the line officers cannot be overemphasized.

In actual jungle warfare unbelievable physical hardships were encountered which added materially to production of battle reactions. Mud was knee-deep, torrential rains, or numerous showers and steaming jungle with impenetrable thick undergrowth, were the typical scenes of the man-hunt. There was no front line. The enemy hid in trees and attacked from all directions. Death lurked around every bend along the vine-covered trails. Men stalked the enemy as a hunter does an animal. The Yellow "animal" was as treacherous as a mountain lion. Raiding parties or squads, the small family group, comprised our tactical units. This vicious, tricky, fanatical foe fought with a frenzy and fury seen only in wounded wild animals when cornered.

There are many other factors peculiar to all theatres of actual combat

that must be mentioned fully to appreciate the underlying mechanism of combat area neuroses. Some are instinctive and inherent, whereas others are acquired, such as poor orientation, inadequate training, poor leadership and lowered morale.

Little need be said about fear in this discussion. The average soldier knows that fear is a normal reaction. He has been told that every normal individual is afraid, and that it is not disgraceful; in fact, it is a desirable attribute. He receives a simple explanation of the biochemical changes produced by fear, and how the body mobilizes adrenalin and glycogen, and how the organism goes on the alert as the result of increased nervous tension. He is told how to master that fear. The primitive herd instinct is explained to him. He understands why he prefers to fight alongside of men whom he knows and trusts. He is taught how to meet the enemy when he is alone, on his own. He knows the enemy is also afraid and he is schooled in how to outguess and outwit his adversary.

Because we have been a nonbelligerent people, and because we lack the fanaticism, hatred, and primitive-destructive drive of the Nazi and Jap, it has been necessary to indoctrinate our soldiers with a bitterness and resentment, and to try to stimulate a hatred for the enemy based upon the atrocities committed on our soldiers and our allies by our ruthless foe. The morale of a fighting force is probably more important than any single factor in the production of neuroses in the combat area. Following are some of the more important factors that affect the morale of a unit adversely.

Competent leadership is most important. There is no place in our Army for an officer who cannot lead his men, fight for his outfit to get better mail service, more amenities and better food. He must share in the hardships and deal firmly but fairly with his command. He must inspire confidence and loyalty in the outfit. He must make his men believe that they have the best outfit in the whole theatre, and his praise for things well done helps more than criticism for the mistakes they make. He quarterbacks the team and runs the plays. Such an officer will carry his group through many a tight place and they will have very few mental casualties. If he is the first to jump into a slit trench and get the jitters, a mass panic may result. Unfortunately, anxiety and panic are highly contagious emotions.

The long inactive periods, awaiting action, the monotony of isolation in a restricted sphere, the lack of mail, or worse still, the receipt of letters from home which worry the soldier, particularly those which describe illness, financial or domestic troubles, are most demoralizing. Letters of complaint, and description of strikes at home, fabulous incomes of the friends who are not in the service, all create resentment and bitterness and make the soldier say, "What the hell am I fighting for?"

Prolonged overseas service with slow promotion, a lack of social and sexual outlet, inadequate entertainment and recreational opportunity have an accumulative effect and establish an insidious background for a real mental "blow-up." We see a progressive irritability and restlessness at first, later a

listlessness, and lack of initiative approaching apathy. When the soldier stops griping there is trouble ahead.

All of these more intangible, yet important phases of a lowered morale, are commensurate with the time the soldier spends overseas. I am doubtful if we can create the necessary spark by any method of indoctrination unless it is combined with a prolonged rest or furlough in some civilized and normal community far removed from battle—preferably home. If it were practical it would be most desirable to remove the entire team as a unit.

The feeling of insecurity provoked by many of the above factors establishes a fertile soil for the superimposed ego regression. Psychoneurotic escape patterns naturally develop in those who succumb to these intrinsic and extrinsic stimuli.

Conclusions

1. As a nation, involved in a global war, we find ourselves fighting *for* others rather than *against* an enemy. We lack the fanaticism, hatred and primitive destructive drive found among those countries either bent on the acquisition of territory and the pillage and destruction of their enemy, or those nations with their back against the wall trying to preserve their homes and prevent the rape and murder of their beloved ones.

2. Our fighting men, as a class more intellectual, consequently more sensitive, and subject to emotional lability, are fighting many thousands of miles from home under conditions of great physical hardship, because of a *sense of duty.* This altruistic motive would be insufficient for a less intelligent people. In spite of all this we have no greater incidence of neuropsychiatric disability than our allies or enemy. We simply recognize and admit their existence and treat them.

3. Acute emotional breaks occur under combat conditions and are the direct result of fatigue, exhaustion, and the strain in combat. Normal people are victimized. Early treatment in the combat areas restores most of these people in a matter of days to a full duty status. The fact that so few cases of this type recur, unless resubjected to similar prolonged engagements under the same conditions, is indicative of a benign illness. The animal organism has suffered both a physical and mental depletion of energy that renders it helpless. Temporarily, these men have reached their elastic limit of endurance and collapse. Rapid revitalization physically and artificially induced mental rest brings about a return of a normally functioning unit. The prognosis is excellent. This condition does not merit the application of a psychiatrically stigmatizing name or term. Even those patients who pass through our chain of evacuation to the zone of interior because of a more prolonged convalescence continue to show improvement as their boat approaches our American shore.

4. Continued improvement and many recoveries take place in our convalescent hospitals and reconditioning centers here at home. We can be extremely optimistic about these cases and can even offer a good prognosis

for most of the less malignant psychoneuroses that show evident preinduction signs of psychological traumata. From experience, we are convinced that we are seeing many more recoveries among our psychoneurotic casualties from overseas than are to be found among the same group of more deep-seated maladjusted individuals who never went abroad. The latter group are more malignant and refractory toward treatment.

5. The increased incidence of psychiatric disorders is often indicative of lowered morale. Factors that lower morale have been discussed.

6. Preventive psychiatry, proper orientation and indoctrination before combat are essential to the maintenance of a high morale and a decrease in the incidence of psychiatric disabilities. The importance of having psychiatric guidance in combat areas is obvious. The rôle of the psychiatrist as a staff officer of the tactical commander must be emphasized.

7. I am convinced we have the finest fighting force, the best informed, the most intelligent, and, therefore, the greatest military power on earth. What we have lacked in zeal and fanaticism, factors which, in the light of the enemy wanton waste of human life, seem stupid, we have gained by intelligent planning and tactical execution, thus conserving the lives of our fighting men and preserving our American way of life.

NEUROPSYCHIATRIC COMPLICATIONS FOLLOWING SPINAL ANESTHESIA *

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The advantages of spinal anesthesia under certain restrictions are so obvious and the results obtained from its use so excellent that one can appreciate the popularity of this valuable anesthetic measure. However, from time to time, there have appeared in the literature reports of patients who have developed neurological complications occurring immediately after or remotely following the administration of a spinal anesthetic. The statements in the literature are extremely contradictory as to the frequency with which such nervous sequelae occur. Emmett [1] reports he had no neurological sequelae in 1415 cases, and Foss and Schwalm [2] state that in 3,000 cases they have never seen the slightest evidence of peripheral neuritis or sensory or motor disturbances. They quote Pemberton to the same effect. On the other hand, White-Morquecho,[3] Peirson and Twomey,[4] Ferguson and Watkins,[5] Hammes,[6] Kammon and Baker,[7] Lindemulder,[8] Hyslop,[9] Brock, Bell and Davison [10] and others have recorded definite instances of neural diseases following the administration of a spinal anesthetic. Hyslop gives 0.5 per cent as the incidence of sequelae in the central nervous system. Jarmen [11] gives the incidence of paralysis as one in 10,000 cases. Loeser [12] believes that an inflammatory syndrome affecting isolated peripheral nerves is more frequent than is realized. He reports five cases in one year. Egorova [13] reports 128 cases of which involvement of cranial nerves took place in 3.2 per cent, sphincter disturbances in 13.8 per cent, diminution or loss of tendon reflexes in 15.6 per cent, and paresis of the lower extremities in 4.6 per cent. These complications were not associated with preëxisting nervous lesions. A review of the literature and the personal experiences recorded by Critchley,[14] and Light and his colleagues [15] suggest that neurological complications occur much more frequently than is commonly supposed. Nervous complications of the most varied types may follow the use of spinal anesthesia. Clinically, the neurological complications display great diversity and range from cranial nerve palsies and peripheral mononeuritis to transverse myelitis and encephalomyelitis. Among isolated cranial nerve paralyses, unilateral or bilateral abducens palsy is most frequent. Involvement of the optic, oculomotor, trigeminal, facial, auditory and hypoglossal nerve has also been reported. Lesions of the cauda equina, myelitis, myeloradiculitis, aseptic meningitis and encephalomyelitis have been recorded. Thus, almost

* Delivered before a Regional Meeting of the American College of Physicians at Philadelphia, December 15, 1944.

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any part of the central nervous system may be affected. A survey of the literature makes it apparent that a wide variety of neurological complications, either immediate or remote, mild or severe, temporary or permanent, may follow spinal anesthesia.

In the past few years we have been concerned with a number of neurologic and psychiatric problems in which the question of a relationship to a previously administered spinal anesthetic was pertinent. We are reporting six personally observed instances of neuropsychiatric complications following spinal anesthesia. We are also describing a case of metastatic spinal cord neoplasm which came to light following spinal anesthesia in which the anesthetic agent was for a while suspected as being the cause of the myelitic syndrome. These cases are presented not as a disparagement of a very valuable, if not indispensable, form of anesthesia, but with the intent to emphasize the necessity of looking for and recognizing complications, and, if possible, preventing them.

Case Reports

Case 1. H. McK., West Jersey Homeopathic Hospital. Syndrome of cauda equina neuritis, conus medullaris and lumbosacral cord involvement immediately after pontocaine spinal anesthesia. Poor recovery after four years.

History. The patient, a male of 48 years, was admitted to the Hospital and was operated on for a ruptured duodenal ulcer on November 6, 1940, under spinal anesthesia. A solution of 1.5 c.c. of pontocaine hydrochloride plus 1.5 c.c. of glucose solution was injected in the third lumbar interspace. The administration of the anesthesia and operation were uneventful. The next day he complained of lack of sensation in his lower extremities. He had incontinence of urine and feces. On examination he was found to have a flaccid crural paraplegia with absence of deep tendon reflexes. His physician found the patient had a loss of all sensory perception up to a point above the symphysis pubis.

Examination. On February 19, 1941 the patient was examined by one of us (H. E. Y.). The cranial nerves were normal. The muscular power, reflex activity, and sensation of the upper extremities and trunk were normal. A flaccid crural paraplegia existed with bilateral foot drop. The patient was able to execute feeble contractions of the sartorius and quadriceps femoris groups of the right thigh. However, the remaining muscle groups, especially the hamstring muscles, were completely paralyzed. There was early atrophy of the involved muscles. The deep tendon reflexes of the lower extremities were absent. The abdominal reflexes were present and equal. The cremasteric and gluteal reflexes were absent. Sensory examination revealed a radicular type of sensory loss in the lower extremities and complete anesthesia of the genitalia and saddle area. There was anesthesia in the radicular zones innervated by roots L–1 to S–5 inclusive on the right. There was hypalgesia and thermhypesthesia in the radicular zones L–1 to L–3 inclusive on the right. Vibratory perception was lost up to the level of the first lumbar dermatome segment. Position sense was lost in the toes of both feet. The anal sphincter was atonic. There was an indwelling urinary catheter in situ with an attached tidal drainage apparatus. Clinically, the patient presented a syndrome of severe cauda equina neuritis with involvement of the conus medullaris and lumbosacral cord.

Laboratory Data. Because the patient had been a painter for 30 years the possibility of lead intoxication was investigated. Repeated blood cytology studies revealed normal findings. Red blood cell stippling was never discovered. Blood and

spinal fluid serologic tests were negative. Roentgenologic studies of the long bones, the sacral spine and the pelvis were all negative. Rectal examination and sigmoidoscopy yielded negative findings. Analysis of blood for lead gave findings which suggested that the patient had a "mild active phase of partially delayed chronic plumbism." The lumbar puncture, done on November 20, 1940, yielded clear, colorless fluid under an initial pressure of 160 mm. of water. The spinal dynamics were normal. The total protein content of the spinal fluid was not determined.

Course. Six months after his operation the patient was again examined. He could now control urination by voluntary effort. He could perceive the sensation of a full bladder. When he got this sensation he could, by compressing his abdominal wall, initiate urination. He also had a return of subjective sensation in his rectum and by straining could effect defecation. He still had a flaccid paraplegia which was complete except for the ability to execute motor movements of a slight degree with the muscles of his right thigh. Bilateral foot drop persisted. He complained of sharp, shooting pains in both legs and, occasionally, in his genitalia. He had developed early contractures of both knee joints. There was atrophy of the posterior thigh muscles and gluteal muscles, more marked on the left side. The deep tendon reflexes were still absent in the lower extremities. The sensory disturbances found at the time of the first examination still persisted. The patient has not been seen since the last examination, but a verbal report recently received states that the man still has a crural paraplegia, more than four years after its inception.

Discussion. The question of plumbism as a possible etiology of the sudden paralytic syndrome was raised by a few of the examiners. However, from the onset of symptoms, almost immediately after spinal anesthesia, which we know can be occasionally followed by neurological complications, we may conclude that the cauda equina neuritis and conus medullaris involvement were directly caused by the toxic action of the anesthetic agent used. The possibility of a preëxisting cauda equina neoplasm, primary or secondary, which may have come to light coincidentally at the time of his operation was ruled out by proper laboratory studies. The course of the neurologic picture in this patient emphasizes the poor prognosis which we may expect in some of the cases of post-spinal anesthesia myeloradiculitis.

Case 2. C. T. B., Jefferson Hospital. Syndrome of conus medullaris and cauda equina involvement immediately after metycaine spinal anesthesia. Poor recovery after two years.

History. The patient, a female of 53 years, was admitted to the Hospital three months after she developed symptoms of numbness of the medial aspects of the buttocks and perineum, together with incontinence of feces and frequency of urination. These symptoms had their inception immediately after an operation for cystocele and rectocele under metycaine spinal anesthesia in June, 1942. The dosage of anesthetic agent used is unknown. Immediately after the operation she had to be catheterized for 18 days and she was incontinent of her feces. Since then she has had urgency of urination, urinary dribbling, "pains" in her vagina, and fecal incontinence.

Examination. On September 23, 1942 the neurological examination disclosed impairment of sensation (pin prick and temperature) over the perianal region, over the perineum, and over the posterior aspect of the upper thighs and buttocks, conforming to dermatome distribution of roots S–3 to S–5 inclusive. This saddle area sensory disturbance was more marked on the right side. Rectal incontinence was present. Clinically, the patient presented a syndrome of cauda equina and conus medullaris involvement.

Laboratory Data. On September 27, 1942 the rectal and proctoscopic examinations disclosed fair tone of the anal sphincters and nothing abnormal in the rectum. Cystoscopic examination at this time revealed a markedly hypertrophied and trabeculated bladder, with evidence of some loss of function of the external sphincter. Cysto-

metric examination revealed a hypertonic rather than a hypotonic bladder. Roentgenologic studies of the lumbosacral spine were negative. Examination of the urinary tract by intravenous urography was negative. Blood cytologic studies and urinalysis yielded normal findings. No lumbar puncture was done, hence no spinal fluid examination was made.

Course. It was thought the patient had a cauda equina syndrome involving the distal sacral roots. In view of the precipitous onset following spinal anesthesia, the disturbance was considered toxic in origin. The patient was seen for reëxamination on March 24, 1943. She complained most of severe burning pain in the vagina which she stated was present since operation. Urinary and fecal incontinence were still present as was the numbness in the saddle area. Her bowels failed to move without a laxative. More recently, she had noticed a heaviness of her feet and difficulty in walking. Examination at this time revealed a weakness of dorsiflexion of the left foot and an absent ankle jerk on that side. The sensory impairment found on her previous examination was less definite. She now displayed a great deal of emotional instability. Her condition was regarded as being psychogenic in origin and she was given electrocerebral shock treatment. With three such treatments no improvement was noted. The patient was readmitted to the Hospital on November 30, 1943 with the previous complaints. Neurological examination again revealed loss of pain and temperature sensation along the inner aspects of the thighs and around the anus (radicular zones S–3 to S–5 inclusive). This finding was unassociated with any muscle atrophy. Proctoscopic and cystometric examinations demonstrated an anal sphincter of normal tone and a hypertonic bladder respectively. Lumbar puncture yielded clear, colorless fluid under an initial pressure of 130 mm. of water. The spinal fluid dynamics were normal. The blood and spinal fluid Wassermann and Kahn reactions were negative. The spinal fluid total protein was 31 mg. per cent. The patient continued unimproved.

Discussion. The immediate onset of bowel and bladder sphincter disturbances following spinal anesthesia makes the conclusion inescapable in this case, that the patient experienced a toxic lesion of the conus medullaris and cauda equina. The peculiar sphincteric disturbances are probably accountable by a conus lesion, whereas her subjective and objective sensory disturbances indicate an element of cauda equina neuritis. As in many cases of a chronic, incapacitating illness, this patient developed psychogenic symptoms which at one time dominated her clinical picture and gave the misleading impression that the entire clinical syndrome might be psychogenic in nature. The possibility of a cauda equina or conus neoplasm was ruled out.

Case 3. L. B., Jefferson Hospital. Syndrome of incomplete thoracic transverse myelitis with spastic crural paralysis immediately after procaine spinal anesthesia. No recovery after one year.

History. The patient, a male aged 57 years, was admitted to the Hospital four months after he developed symptoms of a spastic crural paraplegia. On October 5, 1943 he had been operated on for a left inguinal hernia at the Cooper Hospital under spinal anesthesia. A solution of 150 mg. of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. Two days after the operation he complained of numbness which descended from the hips to the toes. He also noticed an inability to move his legs which became progressively worse. After his discharge from that hospital he soon discovered he could not move his legs at all. The numbness persisted. No bowel or bladder dysfunction developed. On February 18, 1944 the patient was admitted to the Jefferson Hospital. He had a spastic crural paraplegia.

Examination. The cranial nerves were normal. The muscular power, reflex activity and sensation of the upper extremities were normal. He had a marked extensor spasticity of the legs. He could not flex the legs and could only feebly flex

the feet. He was unable to walk except with crutches. The patellar and Achilles tendon reflexes were overactive. He had bilateral ankle clonus but no pathological reflexes. Pain, temperature and vibratory sensation was lost below the fourth thoracic dermatome segment on the right and below the fifth thoracic dermatome segment on the left. Position sense was impaired in the toes of both feet. The saddle area was involved in the sensory loss.

Laboratory Data. Lumbar puncture at the Cooper Hospital on November 29, 1943 yielded clear, colorless fluid under an initial pressure of 148 mm. of water. The spinal fluid dynamics were normal. The Pandy test was negative. The spinal fluid cell count revealed two red blood cells and one white cell per cu. mm. The blood and spinal fluid Wassermann reactions were negative. At Jefferson Hospital roentgenologic studies of the cervicothoracic and lumbosacral spine were negative. Repeated lumbar punctures failed to give any evidence of fluid block. The spinal fluid total protein was 70 mg. per cent. The blood cytology, blood chemistry and urinalysis studies were negative. The blood and spinal fluid serological tests were negative.

Course. There was no improvement or progression in the patient's clinical picture during the year following its inception.

Discussion. The patient developed a spastic paralysis which appeared immediately after spinal anesthesia. He stated his symptoms progressed for five to 10 days and then became stationary. At the time of this report he had an incomplete transverse myelitic syndrome at the T–4 and T–5 spinal cord level. Possible spinal cord neoplasm, syphilitic myelitis and intramedullary hemorrhage have been excluded. The obvious diagnosis remaining is that of spinal anesthesia toxic myelitis.

Case 4. M. S., Jefferson Hospital. Syndrome of primary lateral sclerosis with spastic crural paraparesis immediately following procaine spinal anesthesia. No recovery after one year.

History. The patient, a female of 48 years, was admitted to the Hospital two months after she developed symptoms of a spastic crural paraparesis. On October 14, 1943 she had been operated upon for a left inguinal hernia at the Cooper Hospital, under spinal anesthesia. A solution of 120 mg. of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. Immediately after the operation she experienced frequency of urination which persisted for a week, then cleared. At the same time her legs felt weak and her calves felt cramped. When she attempted to get out of bed her legs felt weak and stiff. The weakness and stiffness persisted and increased in degree. On January 24, 1944 she was admitted to the Jefferson Hospital.

Examination. The cranial nerves were normal. The muscular power and reflex activity of the upper extremities and trunk were normal. There was a marked extensor spasticity of her legs, more marked in the left leg. She was barely able to walk because of the spastic paraparesis. The deep tendon reflexes were hyperactive in the lower extremities and there were bilateral Chaddock's and Babinski's signs present. The abdominal reflexes were absent. All sensory modalities were preserved.

Laboratory Data. Lumbar puncture yielded clear, colorless fluid under an initial pressure of 110 mm. of water. Spinal fluid dynamics were normal. One cell per cu. mm. was found. The spinal fluid total protein was 46 mg. per cent. The blood and spinal fluid Wassermann and Kahn reactions were negative. Blood cytology, chemistry studies and urinalysis were negative. Roentgenograms of the lumbosacral spine and pelvis were normal. To rule out the possibility of an existing spinal cord tumor spinal lipiodol myelography was performed. This study failed to reveal any spinal canal block.

Course. One year after the onset of her spastic paraparesis she showed no recovery. Her disability was as marked as when she was first examined.

Discussion. There can be no doubt that the patient experienced a post-spinal anesthetic toxic myelopathy. The interesting feature is the production of a clinical syndrome of a primary lateral sclerosis with only pyramidal tract involvement.

Case 5. A. K., Jefferson Hospital. Onset of hysterical "paralysis" of lower extremities one year after spinal anesthesia. Experience during spinal anesthesia utilized in the hysterical conversion mechanism. Good recovery with sodium amytal narcosis.

History. The patient, a female aged 31 years, was operated upon April 26, 1943 for an acute gangrenous appendicitis and a papillary cystadenocarcinoma of the right ovary, under continuous spinal anesthesia. The initial dose of the anesthetic was 100 mg. of novocaine. In all, she received 450 mg. of this drug. The administration of the anesthesia and the operation were uneventful. She was readmitted to the Hospital on August 9, 1944 with the history that in February, 1944 she developed an inability to walk. She became extremely apprehensive, developed pain over the precordium and was possessed with the fear that she would never be able to walk again.

Examination. The patient was reluctant to get out of bed to walk. When she did, her gait was a bizarre shuffling, twisting one which has been described as hysterical astasia abasia. The motor power in all her extremities was preserved. The deep tendon reflex activity was normal in her lower extremities. All the sensory modalities were preserved. Emotional instability was marked.

Laboratory Data. The blood cytologic and urine studies were negative. The blood Wassermann reaction was negative. The electrocardiographic tracings were normal. Roentgenograms of the lumbosacral spine revealed no abnormalities.

Course. When the history was presented the possibility of a delayed spinal anesthesia toxic myelitis was entertained. However, the neuropsychiatric examination made it obvious that we were dealing with a case of anxiety neurosis in which the patient had developed a hysterical "crural paraparesis." In talks with her it became clear that she had unconsciously utilized her spinal anesthesia experience in the past in the psychogenic formation of her present gait disability. Sodium amytal narcosis was utilized in the psychiatric treatment of her condition. One narcosis session was sufficient to clear her hysterical gait disturbance. With further psychotherapy the patient recovered from this disability.

Course. The case is interesting in that it indicates how an emotionally unstable individual may utilize the experience under spinal anesthesia later to develop a hysterical "paralysis" of the lower extremities.

Case 6. H. T., Jefferson Hospital. Onset of hysterical "spastic paresis" of lower extremities immediately after spinal anesthesia. Good recovery with electrocerebral shock therapy.

History. The patient, a female aged 32 years, was operated upon August 14, 1943 in the Cooper Hospital for a chronic inflammatory pelvic condition under spinal anesthesia. A solution of 10 mg. of pontocaine dissolved in 10 per cent glucose was injected in the third lumbar interspace. Two days after the operation she developed a sensation that the toes of her feet were trying to curl under. Shortly thereafter her legs became stiff. When she tried to walk her legs were stiff and weak. At times she developed chronic tremors of both lower extremities. The spasticity of her legs seemed to increase and the episodes of clonic tremors of her extremities occurred more frequently. She had innumerable other somatic symptoms such as numbness of her feet, itching sensations, tachycardia and insomnia. She was admitted to the Jefferson Hospital on March 28, 1944.

Examination. The patient walked with a stiff-legged mincing gait which was certainly not the gait of a spastic paraparesis. Motor activity was normal in all muscle groups. The reflex activity was increased in all the extremities, but equal. There were no pathological reflexes. All sensory modalities were preserved. On

numerous occasions she developed clonic tremors of both lower extremities while in bed. The patient was very tense and apprehensive. It was felt she was suffering from hysteria and her gait difficulties were in the nature of conversion phenomena.

Laboratory Data. Blood cytology and urine studies were negative. The blood Wassermann reaction was negative. Because of her acute anxiety state no spinal tap was done.

Course. The patient was suffering from a severe psychoneurosis precipitated by a complicated psychosexual conflict. Her conversion syndrome was no doubt conditioned by her subjective experiences under spinal anesthesia. Sodium amytal narcosis therapy was attempted but did not achieve desired results. Her incapacitation was so great and her conflict so fixed that she was subjected to electrocerebral shock therapy. After five such treatments her syndrome cleared. With psychotherapy she has maintained her improvement.

Discussion. This case is similar to the preceding one except that the conversion occurred almost immediately after the spinal anesthesia. Again, a patient with psychogenic illness conditioned her hysterical gait upon her previous subjective experience with spinal anesthesia.

Case 7. E. M., Jefferson Hospital. Syndrome of radicular pain and rapid progression of a transverse myelitis a week following procaine spinal anesthesia. Suspicion of toxic anesthetic myeloradiculitis. Real etiology metastatic bronchogenic carcinoma to coverings of cord and brain.

History. The patient, a female of 53 years, was admitted to the Jefferson Hospital three months after the removal of her gall-bladder at the Cooper Hospital. She was operated on under spinal anesthesia. A solution of 150 mg. of procaine dissolved in spinal fluid was injected in the third lumbar interspace. The administration of the anesthesia and the operation were uneventful. After the operation she developed sharp pains in the back and right extremities. Two weeks later she noticed numbness of the legs. At about this time she developed weakness of the lower extremities. The numb sensation ascended to the lumbar region and she became incontinent of urine. With the onset of the paralysis of her legs she had burning and tight constricting sensations around her upper abdomen. She was returned to Cooper Hospital and finally transferred to Jefferson Hospital. Additional history was then obtained that the patient had severe back pain which appeared at the same time as her right upper quadrant pain prior to her operation. The suspicion was entertained by her physician and surgeon that she had experienced a myelitic syndrome due to the toxic action of the spinal anesthesia.

Examination. The patient was sensorially clouded and her responses slow and confused. There was marked weakness of the muscles of the arms and hands. She had a complete flaccid paralysis of her legs with absence of all deep tendon reflexes. There was complete loss of all sensation below the level of the fourth thoracic dermatome level. Position sense was absent in the toes of both feet. She was incontinent of urine.

Laboratory Data. Blood cytology studies revealed a severe secondary anemia. The blood calcium level was 10.2 mg. per cent and phosphate was 2.2 mg. per cent. Spinal puncture yielded a small amount of gelatinous, xanthochromic fluid which clotted on standing. The initial pressure was 40 mm. of water. Spinal fluid dynamics indicated an almost complete block. Roentgenograms of the lumbosacral spine were negative. Films of the skull showed the presence of several metastases to the calvarium. Films of the right femur revealed the presence of a pathologic fracture through the upper third of the femoral shaft.

Course. On review of her history and neurological findings an extramedullary metastatic malignancy was immediately suspected. The history of radicular pain antedating her spinal anesthesia, the rapid clinical progression of her myelitic syn-

drome, and the debility of the patient indicated a rapidly extending lesion such as a malignancy to the coverings of the spinal cord. The mental picture of the patient also directed attention to the possibility of metastasis to the brain. The patient became stuporous and died four days after her admission.

Necropsy. The important finding at necropsy was a bronchogenic carcinoma of the right upper lobe of the lung. There were metastases to the mediastinal, lower abdominal and pelvic lymph nodes, to the liver, kidneys, fourth and eighth thoracic vertebrae, left ilium, right femur and skull. Neuropathological study revealed a metastatic lesion in the left frontal lobe of the brain and the dura of the spinal cord was infiltrated with a hard firm neoplastic mass. This metastatic neoplastic dural infiltration was most marked at the level of the ninth thoracic spinal cord segment.

Discussion. When the patient was observed by us the diagnosis of a metastatic malignancy to the spinal canal was not difficult to make. However, the case is a good example of the concomitant spinal lesion that may exist, or preëxist, when spinal anesthesia is given. The fact that a neurological syndrome appears shortly after the administration of spinal anesthesia does not permit omitting a thorough investigation for other possible etiologies.

Comment

In all of the first four cases whose postanesthetic toxic neural complications were definitely established, the cocaine derivative used was known; one received pontocaine, two procaine and one metycaine. The sites of injection were the lumbar subarachnoid spaces between the third and fourth lumbar vertebrae or lower. In this series there was an instance of transverse myelitis, two cases of cauda equina neuritis and conus medullaris involvement and a case of pure pyramidal tract involvement. The time elapsing between the spinal anesthesia and the appearance of the neural complications was almost immediate in all cases. In one of the four cases the neurologic disturbances appeared within two to five days after the anesthetic.

Clinically all of these cases of post-spinal anesthetic neural complication showed little recovery after periods ranging from one to four years. The spinal fluid showed no characteristic picture. There was no pleocytosis or increase in spinal fluid total protein except in the third case.

One of our reported cases emphasizes the fact that occasionally spinal anesthesia may be falsely accused of causing neurological disturbances. This fact is further illustrated by the case reported by Pemberton.[16] Two of the cases in our series are presented to indicate the type of psychiatric complication one may encounter after spinal anesthesia in individuals predisposed to develop conversion hysteria immediately or remotely after their anesthesia experience.

Clinical Sequelae. Stimulated by these experiences, we investigated the literature to determine the various reported neurological sequelae of spinal anesthesia. Hyslop has grouped the nervous sequelae according to whether they are of a focal or a general character, the former being subdivided into the remote and the adjacent types. For the purposes of this report it might be best to discuss the neurological syndromes in their approximate order of frequency.

Headache. Headache is one of the most frequent complications of either spinal anesthesia or lumbar puncture. With Critchley we feel that this symptom occurs so often as scarcely to warrant its inclusion among the true neurological complications. Light and his coworkers,[15] from a survey of many articles, report the incidence of headache ranges from 0.1 to 83 per cent. The majority fall within the range of 1 to 25 per cent, comparable to that following lumbar puncture. It appears that headaches after spinal anesthesia seem to differ from the post-puncture headache in their greater frequency, in a greater liability to a severe and protracted course, and in the occasional development of complicating features, such as meningism or cranial nerve palsies.

Cranial Nerve Involvement. Paralysis of the abducens nerve constitutes, according to the literature, the commonest nervous complication. In 1906, Becker [17] and Landow [18] reported such cases. In 1910 Reber,[19] in addition to his own cases, reviewed the literature and found 36 cases at that time. Blatt [20] in 1928 had collected 78 cases of abducens palsy following spinal anesthesia, and during the same year, at the Surgical Congress in Paris, 10 additional cases were reported, making a total at that time of 97 cases in all. Since 1928, approximately 30 cases have been reported. In 1937 Critchley reported two such cases. Hayman and Wood [21] reported two cases in 1942. Critchley's cases are typical of those reported in that the paralysis developed some days after the anesthetic, in association with severe headache. In both cases the ocular paresis was bilateral, although unilateral cases have more often been reported. Anderson stated that abducens paralysis may occur in from a few minutes to two weeks after the time of the injection of the anesthetic agent. It may be accompanied by photophobia as in some of the cases of Fawcett.[22] Chiene's [23] 30 cases varied in onset from the ninth to the twelfth postoperative day and the duration was from three weeks to six months. Ashworth's [24] patient completely recovered in eight weeks. In the cases of Rollet and Berard [25] the paralysis lasted for from one week to four months. In Hayman and Wood's two cases the palsy cleared in about three weeks. Hence, one can conclude that this lesion is usually transient and clears up in the course of a few days to months.

Other cranial nerve palsies have been occasionally reported. Jacqueau [26] has recorded optic atrophy and White-Morquecho [3] described transitory amaurosis in a case. Other authors have recorded lesions of the trigeminal, facial, auditory, and hypoglossal nerves. Paralysis of the seventh, eighth, and ninth cranial nerves has been observed by Angelescu and Tzovaru.[27]

Cauda Equina and Conus Medullaris Lesions. This type of sequel has been recorded frequently in the literature. Both Critchley and Ferguson point out that the syndrome is one which might easily be overlooked, especially when represented chiefly by urinary retention and sacral analgesia. Thus, White-Morquecho reported 19 cases of slight bladder paresis and anal incontinence in six patients, in a series of over 3,000 cases of spinal anesthesia. Egorova in a collection of 180 cases found sphincter disturbances

in 13.8 per cent and a diminution or loss of the deep tendon reflexes of the lower extremities in 15.6 per cent. Critchley reported eight cases and Ferguson and Watkins recorded 14 cases characterized by bowel and bladder sphincter disturbance, and signs such as sacral sensory loss and alteration in the tendon reflexes of the lower extremities. More recently, Peirson and Twomey [4] have recorded a case and reviewed the literature. They point out that in these cases the most striking and most serious symptom was immediate retention of urine, followed at a later period by incontinence. The patients continued to have residual urine and difficulty in urination for periods varying from several weeks to more than two years. The less serious symptoms in this group (although it was the most serious in our patient, C. B.) consisted of loss of anal tone, an area of saddle anesthesia and diminution or absence of the deep tendon reflexes of the legs. In some cases cystometric and cystoscopic studies were made after a period of several months and the patients were found to have trabeculated, hypertonic bladders, associated with a variable amount of residual urine. Ferguson and Watkins found that complete urinary retention developed after operation in all their 14 cases except one whose bladder disturbance was incontinence on one occasion. The period of complete retention varied from about one week to a month, and was followed by incontinence. The latter was usually of short duration (a few weeks), but in two cases was still present after more than two years. Incontinence of feces lasted less than one month in six cases. In three patients it lasted about three months, and in one about six months. A sense of numbness in the saddle area was still present in some of the patients three years after operation. In three of Critchley's eight cases the symptoms of this syndrome showed some clinical evidence of improvement in three weeks; in four others, however, symptoms persisted without change up to the time of death. Brock, Bell and Davison's fifth case regained the ability to take a few steps five months after the onset, but the sphincters and sensory and reflex status remained unchanged. This evidence of permanent damage is present in the two cases reported by us. Kamman and Baker [7] reported similar experiences in three cases, as have Silva [28] and Boisseau.[29]

Neuritis and Radiculitis. Loeser [12] has reported five cases of peripheral neuritis affecting isolated peripheral nerves which he had seen in one year. He is of the opinion that this is a more frequent complication than the literature would indicate. In his series of cases, three had involvement of the ulnar nerve, one of the sciatic and one presented paresthesias and sensory changes of both lateral cutaneous nerves of the thigh. He felt the original process was an arachnoiditis, the inflammatory process extending to the cord and ultimately involving the peripheral nerves from one to three weeks after the administration of anesthesia. Brock, Bell and Davison in their series include a case of lumbar radiculitis which appeared three weeks after the spinal anesthesia. Jones [30] has reported a case of sciatic pain lasting six months. Critchley described a case of sacral radiculitis which came on 24

days after the anesthesia. Lindemulder [8] regards pains in the extremities as constituting the commonest sequel. In three of his cases pain in the legs persisted for several months and was associated with marked tenderness of the muscles. As a rule, in most of these reported cases, the symptoms improved gradually and full recovery occurred. Many writers, such as Blatt, Dassen,[31] Anderson [32] and Critchley, report the presence of lancinating pains, anesthesias and trophic changes. However, in these cases there was usually evidence of a more widespread morbid process affecting the roots and cord, in the nature of a myeloradiculitis. Anesthetic areas of the body may be the site of complicating trophic disorders including, of course, severe bed sores. Hyslop has described two cases in which a herpetiform eruption appeared over the lumbar dermatomes after spinal anesthesia.

Myelitis, Meningomyelitis and Myeloradiculitis. In a smaller group of reported sequelae there is evidence of a more widespread morbid process affecting the cord, and, on occasions, the meninges and roots at a higher level. Cases of transverse, diffuse or ascending myelitis have been reported following spinal anesthesia. Smith [33] observed a complete transverse myelitis in the ninth thoracic segment which appeared on the seventeenth postoperative day. Franke [34] described two such cases with permanent paralysis. Degenerative myelitis has been reported by Nonne and Demme.[35] Devraigne and his co-authors [36] had a case of quadriplegia of transient duration following anesthesia. Maclachlan [37] has recorded a case of disseminated encephalomyelitis and Donovan and his collegues [38] have described a case of meningomyelitis following spinal anesthesia. In the fifth case reported by Brock et al. a toxic myelopathy occurred. Necropsy revealed apparent softening of the cord at the twelfth thoracic and first lumbar levels. Over a wider longitudinal extent there were found changes in the myelin sheaths, axis cylinders and glia, most marked at the periphery and also at the root-entry zones. Hewer [39] described a patient who developed a myelitic syndrome after percaine anesthesia. Nine months later a laminectomy was performed revealing a constricting band of adhesive arachnoiditis around the lower part of the spinal cord and the upper portion of the cauda equina. Improvement occurred after operation. Kamman and Baker have recently reported a case of flaccid paraplegia immediately following spinal anesthesia which resembled a similar case recorded by Koster and Weintrob.[40] The necropsy on the patient of Kamman and Baker disclosed an adhesive leptomeningitis of the middle and lower thoracic spinal cord. In some areas this membrane had become hyalinized. In this area of the cord the posterior columns were replaced by a large area of softening. The remaining white and gray matter was severely damaged. Demyelinization was prevalent in the posterior and lateral columns of the lower thoracic, lumbar and sacral segments of the spinal cord. Hammes recorded two cases which manifested themselves with a syndrome of a slowly ascending myelitis. Both developed evidences of spinal fluid block. One of the cases was explored and a dense pachyleptomeningitis was found for the entire distance of the cord exposed

at laminectomy. Hammes concluded that inflammatory and fibrotic changes had developed in the meninges due to the anesthetic. An extension of this process with subsequent involvement of the spinal cord circulation explained, he thought, the clinical syndrome of a slowly ascending myelitis. Brain and Russel [41] reported a somewhat similar case following spinocaine anesthesia. The spinal fluid was normal eight weeks postoperatively. The patient died 16 weeks later and pathologic examination revealed a massive softening of the spinal cord up to the twelfth thoracic segment, with inflammatory reaction in the pia, and perivascular changes. Another example of this type of complication is offered by the sixth case in the series reported by Brock et al. This patient developed a cauda equina neuritis following spinal anesthesia. During the next 29 months a transverse myelitis and radiculitis developed, which ultimately proved fatal. The clinical course was characterized by long periods during which the condition was stationary. With subsequent exacerbations higher levels of the cord become involved. They suggest that the original chemotoxic effect on the spinal cord by the anesthetic may have devitalized the neural tissue so that other factors, such as a dormant virus, may have become active and caused further involvement.

Focal Cerebral Lesions. It is difficult to say in any case in which hemiplegia occurs after spinal anesthesia that it was definitely due to the anesthetic agent. Critchley described a patient who developed mental symptoms and a transient hemiplegia immediately following spinal anesthesia. He suggested the possibility of cerebral angiospasm or a small thrombosis, due in part to an associated vascular disease. Behrend and Riggs [42] and Watter [43] reported similar cases. The first authors felt the sequel was due to a relative cerebral anoxia produced by an alteration in blood pressure occurring as a result of the effect of the surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency. Watter stressed the factor of stagnant anoxia caused by spinal anesthesia as the precipitating factor. Other cases of hemiplegia following spinal anesthesia have been recorded by Arnheim and Mage,[44] Schreiber,[45] Bona [46] and Yamanuti.[47]

Meningitis. The occurrence of meningitis following spinal anesthesia is perhaps the most easily explained of all the complications and can be prevented by aseptic technic.

Aseptic meningitis following spinal anesthesia has been recorded by Brock, Bell and Davison in the same way as it has been reported very occasionally as a complication of simple lumbar puncture (Reynolds and Wilson [48]).

Neurological Disease Precipitated by Spinal Anesthesia. Preëxisting disease of the central nervous system is given as a contraindication to spinal anesthesia by some authors. It is a well recognized fact that the first clinical manifestations of some clearly defined nervous disorder may date from a severe trauma, operation or confinement. It is an accepted fact that cerebral trauma may precipitate, aggravate or accelerate the degenerative process of general paresis or cerebral arteriosclerosis. Spinal anesthesia may also be

a precipitating agent in the evolution of certain neurological affections. Hammes,[6] based on his experience, concludes that the depressing effect on the circulation of the anesthesia and the hemolytic and myelitic action of the toxic drug may hasten an underlying degenerative process and increase the clinical symptoms. Critchley cites a case of multiple sclerosis and another of progressive muscular atrophy the first signs and symptoms of which came on almost immediately after spinal anesthesia. Synder and Synder [49] record a case of meningovascular syphilis which flourished clinically immediately following the anesthetic experience. Other instances of acute onset of central nervous system syphilis after spinal anesthesia are reported by Faure-Beauhieu,[50] La Cava,[51] and Donovan and colleagues.[38] Hammes also reports two cases of neurosyphilis (tabes dorsalis and paresis) which were precipitated by spinal anesthesia. This author admits that he has observed several patients with tabes and one with cerebrovascular syphilis who did not show any increase in the neurological syndrome following spinal anesthesia for abdominal surgery. In his paper Hammes also records a case of multiple sclerosis and one of posterolateral sclerosis, secondary to pernicious anemia, where the clinical progress was unusually rapid and marked following spinal anesthesia. Although no definite conclusions can be drawn as to the causative relationship, these cases demonstrate that the chemotoxic effect of the various spinal anesthetics may precipitate symptoms and aggravate preëxisting neurological disease.

Pathogenesis of the Neurological Sequelae. Numerous observers and experimenters have reported the postmortem changes in the central nervous system following spinal anesthesia. Pathologic changes have been reported by Nonne and Demme, Spielmeyer, Lindemulder, Maclachlan, Brock, Bell and Davison, Brain and Russel, and others. The lesions observed are usually degenerative changes in the cord, demyelinization and atrophy with evidence of glial reaction, together with a varying degree of meningeal reaction. Myelomalacia was found in the cases reported by Brain and Russel and by Kamman and Baker. Chronic adhesive arachnoiditis and pachymeningitis have been present at necropsy associated with the above findings of toxic myelitis.

From the experimental work done there is positive evidence that various cocaine derivatives have a toxic destructive effect on nerve tissue when injected intrathecally. Wossidlo [52] found changes in the nerve cells up to 24 hours after subarachnoid injection of procaine in rabbits and dogs. Transitory changes in nerve cells had also been reported by Van Lier.[53] Davis and his associates,[54] after injecting a series of common anesthetic substances intrathecally in dogs, found various changes which made them conclude that these drugs had a hemolytic and myelolytic action on the spinal cord. They reported the following changes:

1. A varying degree of meningeal inflammation as a constant finding.
2. Changes in the ganglion cells.

3. Swelling and fragmentation of the axis cylinders with degenerative changes in the fiber tracts. It was noted that the degenerative and cellular changes were inconstant in animals allowed to live 90 days or more but that the meningeal reactions were constant and marked. Spielmeyer [55] had previously reported essentially similar observations in his experimental animals and had concluded that there was a direct toxic action on the axon cylinders with subsequent secondary retrograde degeneration of the ganglion cells. In line with his conclusions are the pathological findings reported by Brock and co-workers in a case of acute myelitis following spinal anesthesia. There was extensive destruction of the myelin sheaths, axis cylinders and glia, mostly at the periphery of the cord and at the zones of entrance of the posterior roots. The ganglion cells of the anterior and lateral horns were also slightly involved. Lundy and his co-workers [56] studied the changes in the spinal cord produced by a dose of procaine sufficient to cause permanent and fatal paralysis. They found peripheral degeneration of the myelin in the anterior, lateral and posterior columns of the spinal cord. Haven [57] in his experiments found an inflammatory reaction of the meninges similar to that which had been reported by Davis and his co-workers, which in the older animals reached a stage of fibrotic scarring. McDonald and Watkins [58] reported that intrathecal injections of spinal anesthetic solutions in cats in concentrations commonly employed clinically, though in relatively larger doses, could produce lasting paralysis comparable to lesions of the cauda equina. On the other hand, Koster and Kasman [59] were unable to demonstrate any pathologic changes in the spinal cord of autumn frogs or in human cords after spinal anesthesia.

In spite of the accumulated reports of postmortem material and experimental work, the question of etiology in many of the neurological sequelae of spinal anesthesia remains unsettled. In most of the cases the neural syndromes so speedily followed the intrathecal injection of the spinal anesthesia as to suggest a direct chemotoxic effect of the cocaine derivatives on the neuroaxis. It must be emphasized, however, that the direct chemotoxic effect does not entirely explain the causation of many of the neural complications. There is the fact that the great majority of patients operated upon under spinal anesthesia do not develop neurological sequelae. Furthermore, the cases reported in which the interval between the anesthesia and the onset of symptoms is relatively long, suggest the possible intervention of other factors. This consideration is also pertinent in the reported cases of remote complications of spinal anesthesia such as isolated cranial nerve involvement or focal cerebral damage. The suggestion is presented by some writers that some of the nervous sequelae are due merely to the activation of a latent morbid process within the nervous system or by activated latent organisms of low toxicity which produce a low grade meningitis. This type of pathologic process might explain the cases in which the neurologic syndrome is progressive after spinal anesthesia. Here one must assume that the original chemotoxic effect permitted other factors (virus?) to operate

on neural tissue devitalized by the anesthetic. Behrend and Riggs emphasize that the anoxia caused by the circulatory depression following the anesthetic may be the underlying factor in the production of cerebral neurological sequelae especially in the presence of impaired cardiocirculatory efficiency. Watter also believes that the stagnant anoxia caused by spinal anesthesia, in the presence of chronic anemia, heavy premedication or other factors which help further to impede the utilization of oxygen, can produce cerebral complications. Brock and his colleagues feel there may be a tissue sensitivity to the cocaine derivatives in certain individuals which predisposes them to the development of neurological complications. There is, of course, no way of determining whether or not a patient's nervous tissues are oversensitive to the cocaine anesthetics.

Summary and Conclusions

Six cases of neuropsychiatric complications associated with spinal anesthesia are reported. Four of these cases occurred immediately following the use of the anesthetic agent and present syndromes of serious myelitic or myeloradicular nature. Little or no recovery occurred in all. Two of the reported cases were in the nature of conversion hysteria "paralysis" of the lower extremities. The conversion mechanism was conditioned by the patient's subjective experience with spinal anesthesia. A case of metastatic spinal cord neoplasm, which came to light immediately following spinal anesthesia, is presented to illustrate the importance of keeping in mind the possibility of preëxisting neurologic disease when evaluating the rôle of spinal anesthesia in the causation of postoperative neurologic sequelae.

From this study it is obvious that neurological complications of great diversity, either immediate or remote, mild or severe, temporary or permanent, may follow spinal anesthesia. Undoubtedly many complications are not recognized and some are not reported in the literature.

Serious complications in normal individuals are relatively infrequent and in properly selected cases spinal anesthesia holds an important and almost indispensable place in the surgeon's armamentarium.

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ATROPHIC ARTHRITIS ASSOCIATED WITH SPLENOMEGALY AND LEUKOPENIA*

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In 1924 Felty [1] reported the cases of five adults who had atrophic arthritis associated with splenomegaly and leukopenia. The age of the patients ranged from 45 to 65 years. Their arthritis was generalized, relatively benign, and of at least two years' duration. All patients had suffered recent, marked weight loss. Each had a palpably enlarged spleen that was firm and non-tender. Three of the five had enlarged axillary, inguinal or epitrochlear lymph nodes, and all had some degree of yellow-brown pigmentation of the skin, chiefly on the exposed surfaces. Four of the patients had a slight microcytic anemia, and their leukocyte counts varied between 1,000 and 4,200. Felty considered that there were two possible explanations for this unusual combination of findings in persons suffering from a very common basic disease: (1) "The several features are manifestations of one pathologic process, caused by a noxa which simultaneously affects the joints, the spleen, and the blood leukocytes (and in three of the five cases the lymph glands)"; (2) "The syndrome is merely the confusion of two separate clinical entities, occurring coincidentally in the same individual." If the second explanation were correct, it would be necessary to assume the arthritis to be independent of the rest of the complex, and Felty thought this to be unlikely "on the law of probability alone." Therefore, he stated ". . . one is more or less forced to the conclusion that this syndrome is a distinct clinical entity, of which the outstanding symptoms are those related to the joints, and the outstanding signs are the enlarged spleen and the blood picture."

Since the appearance of Felty's paper 23 cases have been reported under the name of "Felty's syndrome." It is certain that a far greater number has been observed. Throughout these records the validity of this syndrome as a distinct clinical entity is challenged, either through expressed or implied uncertainty. Unfortunately much of the material presented, and this includes all of Felty's original cases, has been studied without benefit of biopsy or autopsy examination. The value of these discussions is correspondingly lessened. In other instances, one of which must be included in the cases to be presented in this report, thorough tissue study has failed to provide a clear explanation of the morbid forces responsible for the clinical observations.

Three patients with the essential features of Felty's cases were seen at Laguna Honda Home in the past year. It is the purpose of this paper to present the clinical and autopsy studies of this group and briefly to review only those earlier discussions that contained pathologist's reports; thus, con-

* Received for publication January 15, 1945.

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clusions may be made that might aid somewhat toward an ultimate sound evaluation of the several features which compose this syndrome.

Case Reports

Case 1. The clinical course of J. C., white male laborer and watchman, was followed continuously at the out-patient clinics of the University of California Hospital and at Laguna Honda Home from June 29, 1933 when, at the age of 53, he was first seen at the Clinics with a complaint of stiff ankles of two and one half years' duration. His family history was without significance. His past and systemic histories revealed that he had had no serious childhood diseases, tonsillectomy at an early age, "rheumatism" in his feet when 29, acute gonorrhea at 20, and again at 49. In the past he had been a "heavy drinker." He still smoked heavily but used no drugs.

In 1931, at the age of 51, he first noted pain and swelling of his left ankle. This was two and a half years after his last attack of acute gonorrhea. During the following two years his shoulders, elbows, ankles, and fingers were affected at times by pain, swelling, redness. Despite an adequate diet he lost 22 pounds between March and June of 1933. During the preceding two years he had received physiotherapy and injections of an unknown material.

His physical examination in June, 1933, showed a rather pale skin without abnormal pigmentation. He was edentulous, his tonsils were absent, and his heart, lungs, abdomen, and spine were normal. He had no enlarged lymph nodes. His forearm and shoulder muscles were moderately wasted. The ankle joints were swollen and showed bony enlargements. All joints of the extremities were stiff; the knees were limited to 90 per cent of normal motion, and the shoulders to 70 per cent. The elbows were partially ankylosed. The fingers showed early deformity. Roentgenographic studies were reported as "atrophic arthritis of the elbows," and a "combination of atrophic arthritis and flat foot." Genito-urinary examination failed to find any evidence of active gonorrhea. His urine was negative, hemoglobin 94 per cent, red cells 4,650,000, white cells 12,320 with normal distribution of cell types, blood Wassermann and Kahn reactions negative.

In November, 1933, he was seen in the skin clinic where a diagnosis of psoriasis was made and Fowler's solution prescribed. His arthritis was treated with six injections of typhoid vaccine in July, 1933; from this time until 1942 he was given repeated series of body bakes and physiotherapy and frequent intravenous injections of ascorbic acid. His course showed periodic improvement and relapse. In November, 1937, his spleen was first palpable, and his leukocyte count, which had previously been between 7,760 and 12,320 was then 1,600 to 3,500. At this time his blood uric acid level was 3.1 mg. per cent, urine negative, phenolsulfonphthalein clearance 62 per cent. Large lymph nodes were felt in the axillae and smaller ones in the inguinal regions. From 1937 until September 1943, he continued to be ambulatory and suffered occasional exacerbations of both his arthritis and psoriasis. During this period a rose bengal test indicated normal liver function; a complete gastrointestinal roentgen-ray series was negative; marrow obtained by sternal puncture showed moderate myeloid hyperplasia; blood platelets were repeatedly reported as normal, though no total counts are recorded; a mild hypochromic anemia and a definite leukopenia persisted.

On September 1, 1943, he "wrenched his right knee." During the next week this became painful, swollen, and intensely inflamed. He was admitted to the Laguna Honda infirmary on September 7 with a fever of 103.6° F. Examination of the head, neck, and thorax was without significant finding. The spleen was firm, non-tender, and extended 10 to 12 centimeters below the left costal margin. Small, indolent lymph nodes were felt in both axillae and in the inguinal regions. The hands were affected

especially by chronic arthritic enlargement of the metacarpo-phalangeal joints; though there was some stiffness of the interphalangeal joints as well, fusiform deformity of the fingers was not prominent. The wrists, elbows, shoulders, ankles, toes, and left knee were stiff in varying degrees, but none of these joints was tender. The hips seemed unaffected. The right knee joint was swollen, red, painful, and hot; there was some extension of the inflammation above the knee both anteriorly and posteriorly. In the next few days the right popliteal area became more indurated, red and tender, and a milder inflammation spread half way up the posterior thigh. Though the leukocyte count was only 2,320, sulfadiazine was prescribed against this apparent cellulitis. The superficial signs of infection subsided moderately during the following week, but induration and tenderness persisted in the popliteal space. The leukocyte count on September 15 was 5,000 with 75 per cent polymorphonuclear cells. On September 18 the patient developed a maculopapular rash, and the sulfonamide therapy was discontinued. On October 3 the popliteal space was clearly fluctuant. The abscess was incised, and 700 cubic centimeters of pus were removed which contained streptococci of unclassified type. Roentgenograms of the knee and femur revealed a chronic arthritis of the joint and no evidence of osteomyelitis of the bone. On October 13 an incision was made from the posterior mid-thigh to the popliteal space, opening all loculated collections of pus. The wound continued to drain, and granulation tissue formed slowly. Streptococci were regularly recovered from the smears. Blood cultures taken September 25, September 27, and October 28 were negative. A Congo red test performed on October 21 showed 63 per cent of the dye remaining in the plasma after one hour. Because of a slightly bloody diarrhea during the first week of November, stool examinations were made; these were negative.

During November and December the patient's course was quiet, the wound was slowly healing, and the drainage was slight. On January 5, 1944 his temperature rose suddenly to 104° F., and he became comatose. He was moderately cyanotic, his neck was stiff, the lower left thorax was dull to percussion, and moist râles were heard there. The abdomen was negative except for the large spleen. All reflexes were hypoactive or absent, and no abnormal reflexes were elicited. The leukocyte count was 2,000. Spinal fluid was under normal pressure, clear, without cells or elevated protein. The patient remained in coma, and the following morning both lungs were full of wet râles. He died later in this day.

The record of his blood studies is given in table 1.

Autopsy. None of the joints was subjected to postmortem study. The heart was of normal size. The coronary vessels were widely patent, and the valves were but slightly sclerotic. There was some patchy fibrosis throughout the myocardium but no evidence of inflammation. The lungs had many adhesions on their surfaces. The bronchi were inflamed and contained purulent material. There was patchy bronchopneumonia in each lung, and in some areas this had progressed to frank abscess formation. The liver weighed 2,600 grams, had a slightly rounded margin, and was pale with a finely mottled appearance throughout. Microscopically the parenchyma was well formed with some slight fatty infiltration. There was no increased portal fibrosis, although in this area there was noted a diffuse leukocytic infiltration composed mostly of rather mature polymorphonuclear leukocytes and a few round cells. The portal blood vessels and bile ducts were normal. One portal vein contained an organized thrombus. The gall-bladder was large and contained stones. The pancreas, stomach, bowel, and bladder were without significant pathologic change. The spleen weighed 1,600 grams. The splenic veins were widely patent, and the arteries were normal. Microscopic examination showed the capsule and trabeculae to be relatively normal, and the pattern of the organ was preserved. The sinuses were not unusually dilated. Around the Malpighian bodies and the central arterioles there was an infiltration of a distinct, homogeneous, eosinophilic material which took the stain for amyloid and which occupied most of the areas of the Malpighian bodies.

TABLE I
Blood Studies of Case 1

Date	Hgb*	Rbc**	Wbc	Pmn	Banded	Small L.	Large L.	Mono.	Eos.	Baso.
8–28–33	13.67	4.65	12,320	70		20		10		
11–24–33	14.50	4.95	7,760	67		18		9	6	
3–13–34	14.25	4.70	7,950	61		38				1
6–11–35	11.60	4.56	11,400	49	16	17		18		
11– 4–37	14.84	4.90	3,500							
11–16–37			1,600		28	24	4	5		
12–28–37			2,650	18		16	56	6	2	
1–11–38	9.96	3.46	1,600	26		12	46	8	4	
1– 7–34	12.70	4.41	2,520	55	7	32		3	3	
1–30–42	11.80	4.19	2,200							
6–15–43	12.00	4.44	3,280	58	34	40	1	1		
6–19–43	12.69	4.63	4,160	25		15	37	22	1	
7–27–43	14.12	4.96	1,840	32		19	42	4	2	1
9– 8–43	12.10	4.37	2,320	51		22	18	8		
9–10–43			3,420							
9–13–43			4,540							
9–15–43			5,000	75		8	13	3	1	
9–17–43			5,140							
9–29–43	11.59		4,460	74		18	7			
10– 1–43			5,520	74	12	13	8	3	2	
10– 4–43			4,160	76	16	11	10	2	1	
10– 7–43			3,160	54		17	21	6	1	1
10–11–43			4,720	49		16	32	2	1	
10–25–43	10.40		5,160							
1– 5–44	6.90		2,000	42		16	33	7	1	

* Hemoglobin in grams per 100 c.c. of blood.
** Red cells in millions per cubic millimeter.

The surrounding stroma showed some fibrosis and scattered plasma cells and lymphocytes; there was no evidence of abnormal cellular infiltration. The adrenals were of normal size with clear cortico-medullary distinction. On section the pattern of these organs was found to be strikingly deformed by the presence of a diffuse infiltration of an amyloid-staining material that mainly occupied the cortex. Much of this material was extracellular and crowded out many areas of the cortical fascicular layers. The medullary tissue was not abnormal. The kidneys were normal on gross examination. Microscopically their capsules appeared smooth, and the glomeruli were for the most part well preserved and without evidence of crescent formation or adhesions. A few glomeruli, however, contained hyalinized tufts which stained as amyloid. The prostate was normal except for rare inflammatory cells. Sections of lymph nodes were taken from many parts of the body. All of these had a well preserved pattern with distinct lymphoid elements. In some areas the sinusoids were rather prominent and contained many cells apparently of the reticulo-endothelial system. Bone marrow specimens were taken from rib, sternum, and vertebral bodies. All of the marrow tissue showed a diffuse replacement by large sheets of relatively uniform cells which were of moderate size with a moderately eosinophilic cytoplasm and usually with vesicular nuclei. These cells were very young, and the absence of more mature cells of their type made their identity uncertain. Occasional polymorphonuclear leukocytes were seen, mature cells of the monocytic series were scant, and only rare lymphocytic cell types were noted. Erythrocytic hemopoiesis was nearly absent; scattered megakaryocytes were seen.

Comment. This case presents several problems. First, the arthritis was of debated type. During the last few years of life this process was quiescent,

and one is forced to consider it from the history and from the impressions of those clinicians who followed the patient's course during the time that the disease was most troublesome. The patient had had two apparently separate attacks of acute gonorrhea, the first when he was 20, the last when he was 49. The first definite arthritis appeared when he was 51; yet in his past history he mentioned "rheumatic pains in the feet" at the age of 29. Gonorrheal arthritis most commonly begins within a few weeks after the onset of the primary attack. However, it is well known that cases do occur many months, and even many years, after the primary infection. No evidence of active gonorrhea was present at the time the patient suffered his most acute joint inflammation. The history of "rheumatic pains" at the age of 29 followed, at 51, by an acute, polyarticular arthritis which affected mainly the smaller joints is quite compatible with a diagnosis of atrophic arthritis. On the bases of the clinical and roentgen-ray appearance of these joints and the course of the affection over a 10 year period orthopedic and medical consultants considered the arthritis definitely to be of the atrophic type.

The second problem is that of the splenomegaly. This is readily explained by the amyloidosis, which was sufficiently widespread throughout the organ to account for its enlargement. However, there remains the question of how best to explain the presence of this amyloid deposit. Several cases have been reported in which chronic atrophic arthritis was found at autopsy to be associated with extensive amyloidosis. These reports include five cases of children afflicted with Still's disease and at least three cases occurring among adults.[2] Other patients in the older age group are mentioned in various discussions concerned particularly with amyloid disease,[3] but in these the type of arthritis is not stated or is uncertain. None of these patients had a history of suppurative disorder, and none suffered from any other disease that is commonly related to amyloid deposit. In two of the adult patients prolonged courses of vaccine therapy were considered, on theoretic grounds, as the possible agent effecting the amyloid response.[4] The patient under present discussion received some injections of an unknown material during his first two years of illness. Subsequently he was given six injections of typhoid vaccine; this was followed by parenteral vitamin C at frequent intervals for a two or three year period. His spleen was not palpable until five years after his first injections and four years after his single course of typhoid therapy. Vitamin C is not an agent which is known to provoke amyloid deposit. It seems unlikely that any of these agents was responsible for the amyloidosis noted in the present case. The patient's final illness, which lasted four months, was dominated by a large suppurating wound that resulted from a streptococcic abscess. Though cases are mentioned in which amyloidosis has developed within periods as short as four months, this experience is decidedly uncommon. Furthermore, since it seems evident that the amyloidosis was the essential cause of the splenomegaly in this case,

it must have been present at least six years before the onset of his ultimate streptococcic infection.

The liver was affected by an apparently chronic, subacute portal hepatitis, but there was no evidence of true portal cirrhosis. As congestion was not present in the spleen, the enlargement of this organ was presumably unrelated to the liver disease.

The leukopenia, moderate anemia, and the microscopic appearance of the bone marrow are not readily explained. Leukopenia occurs in otherwise uncomplicated chronic atrophic arthritis in percentages estimated from 0.5 to 22 depending upon the strictness with which the term is defined.[5] Anemia is more common. The large numbers of young cells in the marrow were of unidentifiable type, but the appearance of the marrow was not that of a leukemia. Maturation of all leukocytes seemed depressed, and evidence of erythrocytic hemopoiesis was scant. The factors responsible for these findings are unknown.

Case 2. M. M., a 75 year old, white, German widow, entered Laguna Honda Home on March 13, 1943 because of incapacitating chronic atrophic arthritis of 20 years' duration. She was born in Germany, and came to the United States in 1913. Her family history was without significance. She used neither alcohol nor tobacco and had taken no drugs routinely other than aspirin.

In her past history there were no unusual childhood diseases. She had had pneumonia in 1920. In 1934 she entered the San Francisco Hospital because of jaundice that followed a year of frequently recurring attacks of severe right upper quadrant pain. There was radiation of the pain to the right shoulder and interscapular region. Her liver was felt two fingers'-breadth below the right costal margin. The spleen was not palpable. A gastrointestinal series was negative, and the gall-bladder failed to visualize for roentgen-ray examination after the administration of oral dye. She had no anemia at this time, but the white cell count was 6,600 with normal distribution of cell types. The jaundice subsided within a week. The patient had many subsequent attacks of similar pain during the following years, but jaundice did not recur. She was again admitted to the San Francisco Hospital in 1936 because of a buccal ulcer that developed after the extraction of several teeth. The ulcer healed slowly, and a biopsy from its edge was reported only as "necrotic tissue." At this entry her liver was not palpable, but the tip of her spleen was felt 10 centimeters below the left costal margin. She had a microcytic anemia, and the white cell count was between 1,000 and 3,500 with 50 to 60 per cent lymphocytes. Pentnucleotide did not alter the cell count. Her blood Wassermann reaction was negative, but the Kahn reaction was positive.

In the systemic history it was stated that in 1923 a private physician treated her arthritis with "iodides, mercury ointment, and malaria" over a two to three month period. The patient could recall no chills resulting from the "malaria." She denied any knowledge of syphilitic infection, and stated that her physician made no mention to her of this diagnosis.

The present illness began in 1923 when she first suffered from pain, tenderness, and swelling in the left shoulder. Soon other joints were affected, and the disease progressed so rapidly that within one year of its onset there was partial ankylosis of both hips and both knees. Therapy was, in general, conservatively based upon rest, diet, and salicylates, but foci of certain and of occult infection were also treated. During a 20 year period nearly all of her joints were attacked by arthritis, and it was finally necessary to admit her to Laguna Honda Home.

Physical Examination. The patient was an elderly white woman with evidence of moderate weight loss. There was no fever. The skin was pale and without abnormal pigmentation. Ears, eyes, nose were negative. The mouth was edentulous, and the tonsils atrophic. There were no abnormal findings in the neck, lungs, or breasts. The heart was of normal size and regular rhythm; a systolic murmur was heard over the entire precordium; a diastolic apical murmur was uncertain. Blood pressure was 150 mm. Hg systolic and 70 mm. diastolic. A smooth, non-tender liver edge was felt 4 centimeters below the right costal margin. The spleen was firm, non-tender, and extended 8 to 9 centimeters below the left costal margin. There were no enlarged lymph nodes. The spine was rigid, with moderate thoracic kyphosis. There was ankylosis of all the joints of the legs with flexion deformity of both knees. The right knee was slightly swollen, warm, and tender. The shoulders and elbows were almost completely ankylosed, the wrists were slightly swollen and stiff, and the fingers, which showed marked fusiform swelling and stiffness, were partially contracted.

Laboratory. Hemoglobin 9.2 gm., red blood cells 3,760,000, white blood cells 1,240 with 32 per cent polymorphonuclear cells, 35 per cent small lymphocytes, 38 per cent large lymphocytes, 2 per cent monocytes. Blood Wassermann reaction was negative, Mazzini positive. Spinal fluid Wassermann negative, Pandy negative, Lange 0000000000. Urine: specific gravity 1.017, faint trace of albumin, no glucose or acetone, no casts, 8 white cells per high dry field. Bromsulfonphthalein test showed all dye to be removed from the blood plasma within 20 minutes. Blood non-protein nitrogen level was 31 mg. per cent. Congo red test at entry found 56 per cent of the dye remaining in the plasma after one hour; this was repeated six months later at which time 74 per cent of the dye remained in the plasma at one hour. The bleeding time was five minutes, and three platelet counts varied from 90,000 to 120,000. Sternal marrow obtained by puncture was too scant for adequate study. Blood cell counts are shown in table 2.

TABLE II

Blood Studies of Case 2

Date	Hgb*	Rbc**	Wbc	Pmn	Band	Small L.	Large L.	Mono.	Eos.	Baso.
6-11-27	10.47		7,200	66		34				
2- 2-34	12.69	4.40	6,600	54		42			4	
10-17-36	8.20	3.40	1,100	35	13	52	12			
10-18-36			1,320	36	10	53	11			
10-21-36	8.20	3.80	2,160	50	43	42	8			
10-24-36			3,500							
10-27-36			2,000							
10-29-36			1,900							
11- 5-36	8.78	3.90	1,000	22	5	78				
3-16-43	9.20	3.76	1,240	32		16	50	2		
4- 7-43	9.04	4.01	1,080	24		35	38	2		
8-26-43	9.24		1,360	26		38	23	5	6	2
9- 1-43	9.04		880	26		58	16			
9-10-43	9.63		470	20		53	19	7	1	
9-11-43		4.85								
9-13-43			580							
9-14-43			920	42		29	17	9	1	2
9-16-43	8.33		1,120	41		29	27	2	1	
9-21-43	8.33	4.07	600	28		38	26	6	6	1
9-28-43	7.85		760	23		42	28	7		
10-13-43	6.90		740	32		21	37	5	3	
10-25-43	8.20	4.08	880	52		7	31	10		
11- 4-43	6.70		1,040	62		24	12	2		

* Hemoglobin in grams per 100 c.c. of blood.
** Rbc in millions per cubic millimeter of blood.

Course. Aside from developing a severe decubitus over the sacrum in May, two months after entry, the patient's condition was unaltered until August 25, 1943 when she suffered an attack of severe, sudden epigastric pain that was maximal to the left of the midline and radiated to the left shoulder. The left upper quadrant and spleen were very tender. The patient had a chill, and her temperature rose from normal to 102° F. The fever and pain lasted seven days; the white cell count on the second day was 1,360. Splenic infarction was considered as a likely explanation.

Two weeks later, September 9, 1943, the patient had a sudden onset of severe pain in the right upper quadrant with radiation of the pain to the right shoulder. She stated that this was similar to her previous "gall-bladder attacks." She had moderate nausea and some vomiting. Her temperature fluctuated between 99° and 103° F. over the next eight weeks. Colic was severe for the first 24 hours, but the pain was dull and of variable intensity after that. Both pain and tenderness persisted to some degree for two months. She had no jaundice, and the urine remained negative. Her white cell count during these last two months varied from 600 to 1,120. Roentgenograms of the abdomen and excretory pyelograms were negative.

During the first week of November she developed abscesses on the lateral aspect of each arm just above the elbows. These may have been related to hypodermic injections of codeine. Fifty to 100 cubic centimeters of pus were removed from each abscess; culture from this material produced *Staphylococcus albus* and hemolytic *Staphylococcus aureus.* On November 10 the patient became stuporous. This progressed to coma, and she died on November 15 with signs of bronchopneumonia in both lungs.

Autopsy. Description of the body was the same as that given above except for increased emaciation. *Heart:* The size was normal, and the valves were competent. The mitral valve contained several atheromatous plaques. There was some atherosclerosis of the coronary vessels. Microscopically the tissues were normal. *Lungs:* The left pleural cavity showed numerous old, fibrous adhesions, especially in the lower portion. The bronchi contained thick, mucopurulent fluid. The right lung was moderately congested; the entire left lower lobe and part of the upper lobe contained numerous confluent zones of consolidation. Microscopically some of the consolidated areas contained small abscesses. *Liver:* The liver weighed 1,600 grams, had a smooth capsule but a mottled appearance. The anterior edges were sharp. By microscopic examination the central veins and adjacent sinusoids were widened and filled with blood. In these areas the hepatic cells were necrotic, and there was mild infiltration with leukocytes. Groups of adjacent liver cells contained large fat vacuoles. Those cells near the portal spaces showed little alteration. *Gall-bladder:* The wall of the gall-bladder was quite thick, dense, and fibrous. The bladder contained numerous pigment and cholesterin stones and thick, turbid brown bile. The fundus of the gall-bladder was adherent to the upper surface of the first portion of the duodenum where, apparently because of pressure of a large stone, there was a fistula of 1.5 centimeter diameter between the gall-bladder and the duodenum. The gall-bladder was also adherent to the gastro-hepatic omentum, which showed considerable scarring. This scar surrounded the portal vein at the point where it received the splenic vein. The latter vein was greatly dilated throughout its length, measuring between 1.5 and 2.0 centimeters in diameter. No thrombosis was present, and no true obstruction could be demonstrated, but it seemed possible that the scarring might have partially constricted this vessel. *Spleen:* The spleen weighed 1,080 grams, was firm, had rounded edges, and much of its lateral surface was adherent to the parietal peritoneum by firm, fibrous bands. The splenic artery was patent throughout, though it was tortuous and moderately sclerotic. There was no evidence of infarction. Microscopically the capsule was normal, the central arteries and arterioles were only slightly thickened, and the lymphoid follicles were small, irregular in outline, and widely scattered. The splenic sinusoids and intersinusoidal

spaces were moderately filled with blood. There was no unusual degree of reticuloendothelial proliferation or fibrosis. The pulp contained large numbers of lymphocytes and macrophages, with fewer eosinophiles and neutrophiles. *Kidneys:* These showed moderate arteriosclerotic changes. *Stomach:* There was evidence of moderate atrophic gastritis. *Intestines:* There were multiple diverticula of the small bowel. *Endocrine Glands:* None of these showed significant pathologic changes. *Aorta:* Marked atherosclerosis. *Left Knee Joint:* The cortex of the bones was thin, and the cancellous bone extremely soft and fragile. The joint was completely obliterated by connective tissue and bony proliferation, and the patella was fused to the anterior surface of the femoral portion of the joint. Microscopically there was seen a small area where an irregular bit of abnormal joint cartilage remained. There was no evidence of residual inflammatory reaction. *Striated Muscle* (left thigh): The individual muscle fibers were indistinct, and both the longitudinal and transverse striations were absent. The few remaining nuclei were long, thin, and atrophic. *Popliteal Nerve:* The nerve consisted mainly of collagen bundles and fat cells. The nerve bundles present were small and atrophic; the myelin sheaths showed considerable vacuolization. *Bone Marrow:* Specimens were taken from the femur and vertebrae. That from the femur was composed largely of congested and hemorrhagic fat and contained a few small hemopoietic foci of both myeloid and erythrocytic activity. The spinal marrow was hyperplastic and contained few bone trabeculae and fat cells. The majority of the cells were of the myeloid series, and all stages of development were represented. Many myeloblasts, promyelocytes, and eosinophilic myelocytes were noted. Cells of the erythrocytic series tended to be scattered rather than arranged in the usual foci, and the nucleated red cells varied greatly in appearance. There were a few typical normoblasts, but the majority had larger, round nuclei of less hyperchromatic appearance. Many of these corresponded with megaloblasts. The number of megakaryocytes seemed to be reduced.

Comment. This patient's arthritis was definitely of the atrophic type; it was chronic, widespread, severe, and associated with progressive emaciation. She had no enlarged lymph nodes, and abnormal pigmentation of the skin was wanting. Microcytic anemia, marked leukopenia, and splenomegaly were persistent during the last seven years of life. The factors that caused the anemia and leukopenia are uncertain, but as in case 1 these findings were associated with a hyperplastic bone marrow that showed evidences of erythrocytic maturation arrest. However, in the present case myeloid hematopoiesis was active in the marrow. A few patients belonging to this general group described by Felty have been subjected to splenectomy because it was thought that the abnormal spleens might have been, in an unexplained manner, responsible for the low white cell circulation and the anemia.

In the present case the leukopenia and splenomegaly developed between 1934 and 1936. In 1933 the patient had frequent attacks of typical gall-bladder colic. Early in 1934 she was studied during one of these attacks that was associated with jaundice. She continued to have occasional bouts of right upper quadrant pain, and this complaint was present rather constantly during her last two months of life. However, the attack in 1934 seems to have been the most severe, and it was the only one during which icterus was present. At autopsy the cholecysto-duodenal fistula appeared to be of relatively recent origin and caused by pressure of a large stone that was still present in the fundus of the gall-bladder. The extreme dilatation

of the splenic vein seemed definitely to be related to the older scarring of the gastro-hepatic omentum to which the gall-bladder was adherent. Pathologic examination of the spleen revealed no abnormality other than typical congestive splenomegaly. It seems logical, therefore, to conclude that the splenomegaly in this case resulted from constriction of the splenic vein by scarring of the gastro-hepatic omentum; the omental scar was an inflammatory reaction to the adherent gall-bladder that had been a focus of chronic infection at least three years before the splenomegaly appeared.

The striated muscle studied in this case is not properly comparable to specimens studied in some cases of chronic atrophic arthritis, for it was taken from the left thigh just above the ankylosed knee joint. Degeneration and atrophy were anticipated findings. The biopsies obtained by Curtis and Pollard[6] from 12 cases of chronic atrophic arthritis were taken from muscle groups remote from affected joints. Their cases were evenly distributed among those with and without splenomegaly and leukopenia. They noted a similar pathologic alteration in nearly all specimens from each group: increase in the interstitial nuclei of the muscle fibers, and small perivascular infiltrations throughout the muscle. They interpreted these changes as evidence that chronic atrophic arthritis is a generalized infectious process rather than a disease that confines its effects to the joints and adjacent periarticular tissues. This concept has long been accepted by Hench and others.

Case 3. D. P., 72 year old white American housewife, entered Laguna Honda Home June 19, 1944 because of incapacitating atrophic arthritis. Her family history was without significance. She had taken no drugs, and had used neither alcohol nor tobacco during her life. Aside from common childhood diseases she had no serious illness other than arthritis. Her systemic history contributed no pertinent information.

Present Illness. In 1911, at the age of 39, she first noted soreness of the feet. Soon the joints of her hands and feet were swollen, red, and painful. Slowly and intermittently other joints were similarly affected. The course of her illness was characterized by remissions and exacerbations of arthritic inflammation. Fifteen years after the onset of her illness her hands and feet became permanently deformed. By 1932 she was bed-ridden and remained so. During these last 12 years she developed severe contractures with increasing skeletal deformity. She followed several dietary regimens without benefit; there was no history of parenteral therapy. In the three months preceding her entry to the hospital her hands, feet, and legs became increasingly swollen, her appetite failed, and she became helpless.

Physical Examination. An elderly white woman, emaciated, with stiff, contracted extremities. She was afebrile. The skin was dry, loose, and non-pigmented. There were numerous decubiti over the body—on shoulders, hips, and buttocks. Examination of ears, eyes, and nose was negative. Snags of a few teeth remained in the lower jaw. The tonsils were atrophic. There were no palpable cervical lymph nodes. The thyroid was not felt. The thorax was symmetrical, and there were a few moist râles at the left lung base. The heart was not enlarged, the rhythm was regular, and there were no murmurs. The liver edge was firm, non-tender, and was felt just below the rib-cage in the right upper quadrant and in the midline. The spleen was firm, non-tender and extended 6 centimeters below the left costal margin. There were small, hard lymph nodes in both inguinal regions. Rectal and pelvic examinations were not performed. The spine was rigid and had a marked thoracic kyphosis. There was muscular wasting in all extremities, and a slight edema of the

hands with more pronounced edema of the legs and feet. The fingers showed marked fusiform deformity with extreme joint destruction; many of the phalanges of both fingers and toes seemed completely disarticulated. Partial to complete ankylosis was present in the elbows, knees, and hips; flexion contractures were present in all extremities.

Laboratory. Hemoglobin 5.85 grams, red blood cells 2,510,000, white blood cells 2,040 with 60 per cent polymorphonuclears (8 per cent of which were banded), 9 per cent small lymphocytes, 18 per cent large lymphocytes, 11 per cent monocytes, 1 per cent eosinophiles, 1 per cent basophiles. Platelets 231,000. Blood urea 60 mg. per cent. Total blood protein 5.68 gm. per cent. Congo red test: 86 per cent of dye remained in the plasma after one hour. Urine: cloudy, specific gravity 1.018, trace of albumin, no sugar or acetone, occasional hyaline and granular casts, 3 white cells per high dry field.

Course. On the day after entry the patient slipped from the side of the bed and fractured her left femur. Two days later she developed râles in both lungs, a fever of 102° to 104° F., and died on June 24, 1944. The day before her death the white cell count was 5,160. Because of her fracture a coroner's autopsy was ordered.

Autopsy. Thorax: Each pleural cavity contained about 100 cubic centimeters of free fluid. *Lungs:* There was a fibrinous exudate over the pleural surface of each lung, evidence of moderate atelectasis, but no sign of pneumonia in the sections studied. *Heart:* This organ was moderately enlarged. The coronary arteries were markedly sclerotic, but no evidence of occlusion was noted. The myocardium showed no discrete scarring. *Liver:* This was not weighed, but was judged to be one and one-fourth times normal size. The edges were rounded. Microscopically there were no cirrhotic changes, but there was moderate cloudy swelling of the cytoplasm of the hepatic cells. *Spleen:* This weighed 700 grams and on gross section was of reddish color, slightly fibrous, and without apparent lymphoid follicles. On microscopic examination the sinusoids were dilated, and there was some swelling and increased prominence of the endothelial cells of the sinuses. There was slight increase in the fibrous tissue elements of the pulp. No siderotic nodules were present. *Kidneys:* These were of normal size. There was an exceptional degree of arterial and arteriolar sclerosis. Within the interstitial tissue there was a diffuse lymphocytic infiltration; many glomeruli were fibrosed and hyalinized. *Adrenal Glands:* These were normal except for a diffuse hemorrhage in one; this was apparently terminal and the result of rupture of a small, sclerotic vessel. *Bone Marrow:* Sections were taken from the vertebrae. These showed mild myeloid hyperplasia with hemopoiesis of myeloid and erythrocytic cell series.

Comment. This patient was observed for so short a time that thorough study was not possible; however, some conclusions are evident. Her arthritis was definitely of the atrophic type, was widespread, and had been present for over 30 years. She had no marked lymph node enlargement, though a few nodes in each inguinal region were palpable. There is no information regarding the time when splenomegaly, anemia, or leukopenia appeared. Her anemia, like that of the previous cases, was microcytic, but it was more severe. No hemorrhagic manifestations were noted, but stool examination and gastrointestinal roentgen-ray studies were not performed. The leukopenia might have been an expression of the degree of anemia; the platelet count, however, was not depressed. The pathological alterations in the liver were moderate and non-scarring. The spleen was slightly congested, but not at all to the degree seen in case 2. These splenic changes

were similar to those of non-specific character described from comparable cases in earlier papers. They will be mentioned below. The bone marrow was slightly hyperplastic, but unlike that of the previous two cases it revealed no evidence of maturation arrest of the cells of either series.

Discussion

In repeated general statements regarding atrophic arthritis Hench [7] has emphasized that it is not a disease that confines its effects to the joints alone but is a generalized affection that causes such diverse results as general weakness and fatigue, functional disorders of the stomach, wasting of muscles that are remote from inflamed joints, and varied reticulo-endothelial system reaction. He has pointed out that ". . . from time to time various names have been attached to the combination of arthritis in association with alteration in the blood picture and with involvement of one or more parts of the reticulo-endothelial system (lymph nodes, liver, spleen). The so-called Felty's syndrome is the latest such syndrome. . . . Felty himself concluded that the syndrome was probably not a new disease, and others have felt that it is merely another pathologic combination of arthritis and reticulo-endothelial reaction, little different from other syndromes reported by Chauffard (1896), Still (1897), and Herringham (1909), and that a new name is, therefore, unnecessary." Chauffard [8] was essentially interested in the appearance of enlarged, tender lymph nodes in a group of patients with atrophic arthritis; white blood cell counts that were taken from this group were normal. Still's [9] cases were among children who had splenomegaly in addition to their atrophic arthritis and enlarged lymph nodes. His patients had either normal or increased white cell counts. Herringham [10] described a boy with Still's disease who also had extreme hepatomegaly. Felty's cases are mentioned above. No thorough studies of biopsy or autopsy material are mentioned in these reports. Singer and Levy [11] have reviewed extensively the world literature concerned with arthritis in association with varied reticulo-endothelial responses.

In 1942 Talkov, Bauer, and Short [12] reviewed all the cases of Felty's syndrome previously reported and described five new cases that could have been classified in the same group. However, they considered that all of their cases and fully 70 per cent of those cases they reviewed strongly suggested the possibility that an accompanying disease unassociated with the arthritis was responsible for the leukopenia and splenomegaly. Only two of their cases were studied post mortem. Among the other three patients, one died of a massive hematemesis that made it "impossible to exclude cirrhosis of the liver with esophageal varices as the cause not only of the fatal hemorrhage but also of the splenomegaly and leukopenia"; one, a girl of 22 who had "apparent rheumatoid arthritis" for 18 months and "slight leukopenia," was subsequently diagnosed as having familial hemolytic anemia; the third had the usual findings of Felty's syndrome when first seen, but when she

was examined four years later "the spleen was no longer palpable, and the leukopenia had vanished, and yet the arthritis had progressed somewhat in severity."

Speculation upon those cases reported without biopsy or autopsy studies is pleasant clinical exercise, but since we are concerned with the problem of whether a circumscribed group of signs is to be interpreted as a syndrome or as the effects of a chance association of two unrelated diseases, it is more profitable to confine discussion to those reports accompanied with pathologists' findings. These will be briefly reviewed.

In 1932 Hanrahan and Miller [13] described a patient who had, in addition to the usual findings, an associated hepatomegaly, urobilinuria, at least one stool strongly positive for occult blood, gastric hypoacidity, and some dyspepsia. Roentgen-ray studies of the gastrointestinal tract were essentially negative. The white cell count varied from 640 to 1,600. A splenectomy was performed, and a biopsy specimen was taken from the free edge of the liver. The spleen weighed 525 grams. Microscopically it showed largely Malpighian bodies and dilated sinuses. The spaces between the sinuses in the pulp were unusually wide and filled with eosin-staining material. The endothelial cells lining the sinuses were enlarged, and the sinuses were filled with large cells showing red cell phagocytosis. Many plasma cells were in the pulp. The liver showed early fatty changes in the central zone with moderate round cell infiltration along the portal vein radicals. This infiltration was limited to the periphery of the lobules where there was a very slight increase in fibrous tissue. It was the pathologist's opinion that these changes are not uncommon in specimens removed from the free edge of the liver. The alterations in the spleen seem non-specific; evidence of chronic congestion is wanting. The patient died 18 months after splenectomy, and, as suggested by Talkov, Bauer, and Short, he may have had cirrhosis of the liver.

Craven,[14] in 1934, reported another case that was subjected to splenectomy. This patient also had a liver that was definitely enlarged, and a bromsulphalein test performed before splenectomy showed 45 per cent of the dye retained in the plasma after 30 minutes and 30 per cent retention after one hour. Eight months after operation there was no dye retention after 30 minutes. Other liver function tests were normal at all times. The microscopic description of the spleen was the same as that noted by Hanrahan and Miller. These changes were regarded as similar to those found in a variety of infectious diseases. A green-producing streptococcus was cultured from a biopsied lymph node. The patient died about 14 months after splenectomy.

Also in 1934 Price and Schoenfeld [15] reported the case of a patient aged 57 who had chronic atrophic arthritis, splenomegaly, pigmentation of the exposed areas of the skin, and a white cell count that varied between 3,100 and 5,300. Liver function tests were normal. The patient was scheduled for splenectomy but died from pericarditis the night before operation. At

autopsy the joints were found to have the typical changes of atrophic arthritis. The liver was normal. The spleen weighed 510 grams and revealed a diffuse fibrosis with dilatation of the splenic sinuses which showed areas of myeloid activity. The spleen was regarded as typical of those described by Ward [16] as chronic septic splenomegaly. In the lungs there were healed and caseating tubercles. It is quite possible that the active tuberculosis in the case was responsible for the leukopenia. It may also have been the cause of the terminal pericarditis and splenomegaly.

Reich [17] reported a case in 1936. The patient was a 21 year old boy who had had "rheumatism" at the age of six. There was no history of subsequent joint pain and no physical evidence of arthritis. He had hepatomegaly and splenomegaly, palpable lymph nodes in the inguinal region, an aortic diastolic murmur, moderate anemia and leukopenia. Sternal puncture was interpreted as showing a "moderate degree of lymphocytic infiltration," and a biopsied lymph node was diagnosed as "chronic catarrhal lymphadenitis." He had a negative blood culture, and all roentgen-rays were negative. He was treated with transfusions and splenectomy. The spleen "was very large and presented the picture of chronic splenitis." The patient died 10 days postoperatively. Reich felt that this patient represented an early stage of Felty's syndrome, and that the causative agent of infection was a *Streptococcus viridans* that could not be isolated. Neither conclusion seems justifiable.

In the same year Singer and Levy [11] described two cases in the course of an extensive review of the problem of etiology in the group of patients described by Still, Chauffard, Herringham, Felty, and others. One of the patients, a man of 55, had typical chronic atrophic arthritis of nine years' duration; he had splenomegaly, enlarged lymph nodes, moderate anemia and leukopenia for at least two years before death. In the last months of illness he was intermittently febrile, had repeated showers of petechial hemorrhages, a blood culture that was positive for *Streptococcus viridans*, and evidence of cardiac decompensation. Subacute bacterial endocarditis seemed evident clinically, though at autopsy his heart wanted any valvular or congenital lesion. The second case was that of a woman aged 49 who was essentially a cardiac patient but who had had atrophic arthritis of the hands for five years. She was observed only during the last four months of life, and enlargement of the spleen was noted only at her final hospital entry two days before she died. When first seen she was treated for acute cardiac decompensation. The following month she developed erysipelas that cleared rapidly. During the last three weeks of illness *Streptococcus viridans* was twice cultured from her blood. She ultimately developed severe chills, an acute sore throat with a yellow-gray membrane over tonsils and pharynx, and agranulocytosis. Her final blood studies showed a red cell count of 1,480,000, hemoglobin 35 per cent, white cell count 450 with 81 per cent lymphocytes and no polymorphonuclear leukocytes. The platelet count was about 42,000. Jaffé performed the autopsies of these cases and submitted

a diagnosis of sepsis lenta on each. Both showed evidence of generalized infection. In each the bone marrow revealed active hemopoiesis of erythrocytic and myeloid cells. There was moderate passive congestion of the liver of the first case; the second showed cloudy swelling and lymphocytic infiltration of the periportal tissue. The heart in the second case had no valvular lesion, but Aschoff bodies were demonstrated in the myocardium. There was no history of rheumatic fever. The spleens weighed 1,710 and 620 grams respectively. Sections of the larger spleen taken from the first case were almost identical with those described by Hanrahan and Miller and by Craven. The smaller spleen showed less cellular hyperplasia of the reticulum but a marked increase in the fibrillar elements; it also contained a large, recent infarct. Cultures made from the spleens yielded a pure growth of *Streptococcus viridans* in the first case and "both a green-producing streptococcus and a hemolyzing streptococcus" from the second case. On the basis of these data and a review of the literature Singer and Levy concluded that cases grouped with Felty's and allied syndromes represent different forms of the same disease, that one disease process is responsible for the varied tissue response noted in these cases, and that the usual etiologic organism is a streptococcus of the viridans type.

Williams [18] also reported a case in 1936. His patient, a man aged 54, had a palpable spleen when first examined. His joint pains had been present for only 10 days, though he had had malaise and intermittent chills over a two month period. He was found to have a polyarthritis, but this was diagnosed by roentgen-ray as of the hypertrophic type. He had a moderate anemia, and his white cell count was between 1,600 and 4,900. Nine weeks after he was first observed he developed an extensive ulceration of the soft palate and tonsillar pillars. At this time his white cell count was 2,500 with 35 per cent polymorphonuclear leukocytes. The ulcers healed shortly. Blood culture was negative. One year later he reëntered the hospital because of soreness of the joints and weight loss. By examination no abnormalities of the joints were noted. His white cell count was 3,300 with 55 per cent polymorphonuclear cells. He died of pneumonia. At autopsy there was an organized pneumonia of the lungs from which *Streptococcus viridans* was cultured. The spleen weighed 260 grams. The Malpighian corpuscles were neither large nor distinct, and the sinuses were inconspicuous. The pulp was highly cellular, containing mainly red cells, lymphocytes, and plasma cells. The liver showed hydropic degeneration. The normal architecture of the lymph nodes was obliterated by a diffuse infiltration with plasma cells. There was a moderate erythroblastic and lymphocytic hyperplasia of the bone marrow but with maturation arrest of the neutrophilic series of cells. The final pathologic diagnosis classified this patient's arthritis as of the hypertrophic type; therefore, the case does not properly belong in the group under discussion. The slightly enlarged spleen showed little pathologic alteration, and the blood dyscrasia is of uncertain type. It does not seem, as suggested by Talkov, Bauer, and Short, to be a malignant neutropenia.

A case of particular interest was described in 1940 by Steinbrocker and Sesit.[19] The patient was observed intermittently from 1928 until 1936. At the first examination he had a polyarthritis of the atrophic type; this had been present in moderate degree for two years. His spleen was just palpable below the left costal margin. Observations during the following eight years indicated a progression of the arthritis, steady enlargement of the spleen so that the tip ultimately reached the iliac crest, appearance of hepatomegaly and general enlargement of the lymph nodes, and periods of low grade fever. His white cell count varied from 2,400 to 4,700 with an apparently normal differential count; anemia was moderate to severe, and the platelet count upon one occasion was 30,000. His last hospital entry was necessitated by increasing dyspnea and anasarca. He died of apparent cardiac and renal insufficiency. In the eight years, the patient was subjected to multiple laboratory tests that returned normal results. Sputum studies and blood cultures were repeatedly negative; the blood uric acid level was normal until the last few days of life when it was 7.18 to 13.0 mg. per cent and the blood non-protein nitrogen was 66 mg. per cent; Congo red tests were normal; three lymph node biopsies were described as revealing the "characteristics of chronic inflammation." Complete autopsy was denied, but sections from the spleen and lymph nodes were permitted. These showed "Hodgkin's disease associated with terminal miliary tubercles." Postmortem studies of the joints could not be made, but by clinical and roentgen-ray evidence the diagnosis of atrophic arthritis seemed definite. The anemia and leukopenia may have been related to either tuberculosis or Hodgkin's disease; the splenomegaly was caused mainly by the latter affection.

In 1942 Lockie, Sanes and Vaughan [20] reported two cases, one of which was autopsied. This patient was a woman aged 53 who had had chronic atrophic arthritis since she was 30. At the time of first observation nearly all joints were affected, she was emaciated, had enlarged axillary and inguinal lymph nodes and palpable liver and spleen. Fifteen months before death she had only slight anemia, and her white cell count was 10,000 with a normal distribution of cell types. Nine months later she had a marked microcytic anemia, and the white cells numbered only 4,200. One month before death her hemoglobin was 50 per cent, red cell count 2,500,000, white cells 1,850 with 54 per cent lymphocytes and 19 per cent monocytes. Terminally she developed ulcerations of the mouth. At autopsy the spleen was found to weigh 380 grams. The splenic follicles were small, the red pulp increased, and the sinuses were prominent, distinctly dilated, and had hyperplastic endothelial cells. Moderate red cell phagocytosis was noted. This is similar to the spleen described by Hanrahan and Miller and others. The liver showed some parenchymatous degeneration. Lymph nodes were altered by non-specific, chronic inflammatory hyperplasia. Bone marrow revealed "slight to moderate myeloid hyperplasia with signs of arrest of maturation at the myelocyte and early polynuclear stages." There were mild inflam-

matory changes in the heart and pancreas. This case was regarded as similar to those previously described in which the findings were of non-specific, generalized inflammatory process.

Steinberg,[21] in 1942, reported three cases, one of which was treated by splenectomy. The patient had lost weight and had become increasingly deformed by her arthritis in the 18 months preceding the operation. She had some enlargement of cervical and inguinal lymph nodes, but the spleen was barely palpable. The white cell count varied from 1,000 to 2,500. Weight of the spleen was not stated. Microscopically the Malpighian bodies were seen to be large, and there were abundant plasma cells throughout. Evidence of superimposed disease was not found The patient's white cell count rose to 16,000 immediately after operation, but three weeks later there was a decline in her general condition and in the blood picture. Details are not given.

In the article previously cited,[12] Talkov, Bauer, and Short reported two cases with autopsy study. The first was a woman aged 64 who had had atrophic arthritis for at least 20 years. She had some abnormal skin pigmentation, marked weight loss, slight enlargement of the cervical and inguinal lymph nodes, palpable liver and spleen. The white cell count varied from 1,500 to 4,300 with a normal differential count; she had a moderately severe microcytic anemia. Thorough study of the gastrointestinal tract revealed no lesion. Blood culture was negative. On the third hospital day she developed fever and pyuria, and *E. coli* was found in the urine. She failed rapidly, suffered multiple decubiti, otitis media, endophthalmitis of the left eye, and died 38 days after admission to the hospital. At autopsy *E. coli* was cultured from the heart blood. The liver weighed 1,900 grams, and showed parenchymal cell destruction, gas bubbles, and large clumps of bacilli. The spleen weighed 675 grams. It contained an old infarct; the normal architecture was indistinct, and the widely dilated sinusoids contained clumps of bacilli; in the pulp there were many polymorphonuclear cells, large mononuclear cells, erythrocytes, plasma cells, and occasional large phagocytes containing red cells. The lymph nodes were altered by the effects of chronic, non-specific inflammation. There were bilateral pyelonephritis, acute and chronic, and acute cystitis. Bone marrow showed a moderate red cell hyperplasia; there were many mature polymorphonuclear cells, but only occasional myelocytes. The joints showed atrophic arthritis. The authors felt that sepsis was the chief cause of death and that the pyelonephritis was chronic with an acute terminal exacerbation. They thought the leukopenia was probably related to the arthritis, but stated that "since splenomegaly is not uncommon in patients with chronic pyelonephritis, the changes in the spleen may have been due, at least in part, to the pyelonephritis, which obviously antedated the clinical evidence of its presence." It is not a common belief that splenomegaly is a frequent attendant upon chronic pyelonephritis.

Their second case was a woman aged 40 who entered the hospital because of symptoms from a large gastric ulcer. She also had crippling

atrophic arthritis, slight generalized lymphadenopathy, splenomegaly, a white cell count persistently below 4,000, and a mild hypochromic anemia. It was established that the splenomegaly and leukopenia were secondary to hepatic disease caused by cinchophen ingestion six years previously. The patient died from peritonitis following perforation of the gastric ulcer. At autopsy the "examination confirmed the suspected cause of death and proved the presence of a healed acute yellow atrophy of the liver, chronic congestive splenomegaly with fibrosis, and rheumatoid arthritis."

Summary

Three cases of chronic atrophic arthritis associated with splenomegaly and leukopenia have been presented together with the complete autopsy record of each. Twelve similar cases reported with biopsy or postmortem studies were reviewed. From this material certain observations may be made regarding the problem of whether this union of clinical findings represents a syndrome, as originally suggested by Felty, or if the majority of these patients are the victims of at least two coincident and unrelated diseases, as argued most forcefully by Talkov, Bauer, and Short.

The splenomegaly of at least four of these 15 cases was clearly caused by a pathologic process unassociated with the general atrophic arthritis. The first case presented in this paper had amyloidosis. References made to the association of amyloid disease with atrophic arthritis indicate not only that the combination is very rare but that a causal relationship between the two affections has not been established. The second patient described in this report had chronic congestive splenomegaly apparently effected by constriction of the splenic vein by scarring of the gastro-hepatic omentum. The spleen of Steinbrocker and Sesit's case revealed the presence of both Hodgkin's disease and miliary tubercles. The second of the cases presented by Talkov, Bauer, and Short had congestive splenomegaly with healed acute yellow atrophy of the liver. Their first case had a spleen of the type described by Ward as chronic septic splenomegaly; however, the infectious process responsible for the splenitis is indefinite. The spleens of the remaining 10 cases showed a similar alteration that was regarded by most authors as a reaction to a non-specific, chronic infection. The third case described in this paper belongs with this group. These latter cases seem to support the contention of Hench and others that atrophic arthritis is part of a generalized infection that affects many tissues including those of the reticulo-endothelial system. The two patients described by Singer and Levy died with *Streptococcus viridans* septicemia. The spleen of their second case was not definitely known to be enlarged until a few days before death; its enlargement may well have been in response to this specific infectious agent. Their first patient, however, had known splenomegaly at least a year before he showed clinical evidence of septicemia. It is not yet possible to accept the suggestion of these authors that *Streptococcus viridans* infection is the probable cause of the Felty and Still-Chauffard syndromes. Their

cases simply indicate that the presence of chronic atrophic arthritis is not a defense against superimposed streptococcus septicemia.

The causes of the leukopenia and anemia noted in these patients remain uncertain. Bone marrow studied in some cases showed hyperplasia with maturation arrest of one or more cell types. Marrow specimens from other patients showed active hematopoiesis, though the clinical course had been marked by severe degrees of anemia and leukopenia. It was for this latter group of patients that Steinberg[21] recommended splenectomy on the supposition that the spleen, through an unexplained mechanism, acted as a barrier between the bone marrow and the peripheral blood stream. No case treated by splenectomy has yet been reported in which the beneficial effects upon the anemia and leukopenia were other than transient, and the postoperative course of these patients was characterized by general decline.

Conclusions

1. Present evidence indicates that splenomegaly and leukopenia when associated with chronic atrophic arthritis do not constitute a distinct clinical syndrome.

2. In a significant percentage of the cases in this group a pathologic process unrelated to that producing the arthritis can be clearly demonstrated to be responsible for the splenomegaly; the cause of the leukopenia is apparent in fewer instances.

3. Thorough clinical observations allied with biopsy and autopsy studies fail, in a majority of the cases, decisively to explain the several features as manifestations either of one pathologic process or as the confusion of two separate clinical entities.

The author wishes to acknowledge the aid received from Drs. A. L. Bloomfield and A. J. Cox, Jr. of the Stanford School of Medicine and Drs. J. F. Rinehart, J. L. Carr, and staff members of the Department of Pathology, University of California School of Medicine.

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OLIGURIA AND ANURIA DUE TO INCREASED INTRARENAL PRESSURE*

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THE author's motive in publishing the results of this investigation was a desire to devise adequate treatment for the great number of victims of crush injury occurring in the war zones. Some weeks before the invasion of France on June 6, 1944, the author sent an extensively documented article to the Headquarters of the Medical Staffs of the Allied Armies which summarized the results of a study begun one year previously (June, 1943). This study led him to recommend a new therapy for two diseases of high mortality frequently occurring in the war zones, crush injury and transfusion kidney. Although the new treatment (which includes bilateral decapsulation of the kidneys) in practically all respects is just the opposite of that recommended in textbooks and current medical journals, an unfavorable reply was received from only one of the Medical Staffs. Subsequently, however, in a letter from the War Office in London, publication of the article was recommended, and later communications stated that the new therapy was accepted and widely used at the time in the British Armies.

The investigation was stimulated by a discussion of the renal lesions in a case of poisoning by mercuric chloride at a Pathological Conference in the Charity Hospital in New Orleans. It seemed to the pathologist conducting the conference and also to the author that no satisfactory explanation had been published for the development of anuria in such a condition as mercuric chloride poisoning, in which there is extensive destruction of tubular epithelium and almost undamaged glomeruli. This is just the reverse of what might be expected when the reabsorptive mechanism is destroyed. It seemed to the author that hitherto insufficient attention had been paid to changes in intrarenal pressure. The question arose, could a change (increase) in intrarenal pressure cause oliguria and anuria?

It seemed practically impossible to devise a satisfactory experiment to test this point in a living mammal. Since urine secretion is believed to be in considerable part a mechanical filtration process, the author constructed a mechanical device ("artificial nephron") by means of which conditions believed to be present in the kidney can be imitated and controlled. The conclusions reached in this article are based in part on observations made with this artificial nephron and in part on a study of autopsy material.

The symptom complex which, the writer believes, results from increased intrarenal pressure, is characterized by oliguria or anuria with consequent hyperazotemia and uremia. The mortality is high, and may reach 65 per

* Received for publication October 20, 1944.

cent in transfusion kidney and nearly 100 per cent in crush injury. For the sake of convenience and brevity the symptom complex will subsequently be referred to as "the syndrome."

The primary factor which makes possible a significant rise in intrarenal pressure is the fact that in adult human beings and in certain animals like the dog and cat, the renal capsule is relatively rigid and inelastic. A relatively slight increase in the bulk of the intracapsular renal tissues may, therefore, cause a significant rise in intrarenal pressure. In small children, on the other hand, and in some animals such as the guinea pig, in which the capsule is relatively elastic, it is probable that the syndrome can not develop.

Among the pathological disturbances which may cause an increase in bulk and a rise in intrarenal pressure are edema, exudate, or neoplastic infiltration of the interstitial tissue, swelling of the tubular epithelium, and dilation of the tubules. The latter may be caused by obstruction of the tubules by solid casts (of necrotic tubular epithelium, hematin, myoglobin, Bence-Jones protein, sulfonamide crystals). These obstructions may be present in the dilated tubules but often they are present in parts of the tubules distal to the areas of dilatation. It is not so much the mechanical obstruction to the outflow of urine which causes the anuria, as the resulting increase in intrarenal pressure. The syndrome may develop in cases in which only part of the tubules is obstructed, or in which no obstruction can be demonstrated. Another relatively benign and transient cause is dilatation of the intrarenal blood vessels as in chronic passive congestion. This may explain the oliguria of congestive heart failure (vide infra).

Such changes are seen in the kidneys not merely in mercuric chloride poisoning, crush syndrome and transfusion kidney, but, in some cases in a large number of other diseases.[30] The same syndrome may be anticipated in these conditions, and further studies along this line are in progress. Associated lesions of the glomeruli may occur, but this does not play an essential part in producing the syndrome. Uremia due to glomerular injury is an entirely different process and must be sharply differentiated.

Dynamics. The artificial nephron (figure 1) is constructed of glass and rubber tubes connected with two mercury manometers and provided with several clamps to control pressure and rate of inflow. Tube c, representing the afferent arteriole, is connected with a water tap to imitate inflowing blood. By adjustment of the water-inflow and of clamp r, the pressure in the afferent arteriole, as measured in manometer u, can be adjusted to any desired level. The effective filtration pressure in Bowman's capsule (tube d) is controlled by clamp s, and measured by manometer e. The proximal convoluted tubule (j), Henle's loop (k and l), the distal convolution (m), and the collecting tubule (n) are represented. The outflow of water at 0 represents urine discharged into the ureter. By adjusting clamp q, a trickle of water can be provided to imitate that reabsorbed by the tubules. Imitation of the malpighian body by a device containing a separating membrane which allowed the filtration of water freely did not change the result. Such a mem-

brane is, therefore, superfluous and merely makes the construction somewhat more complicated.

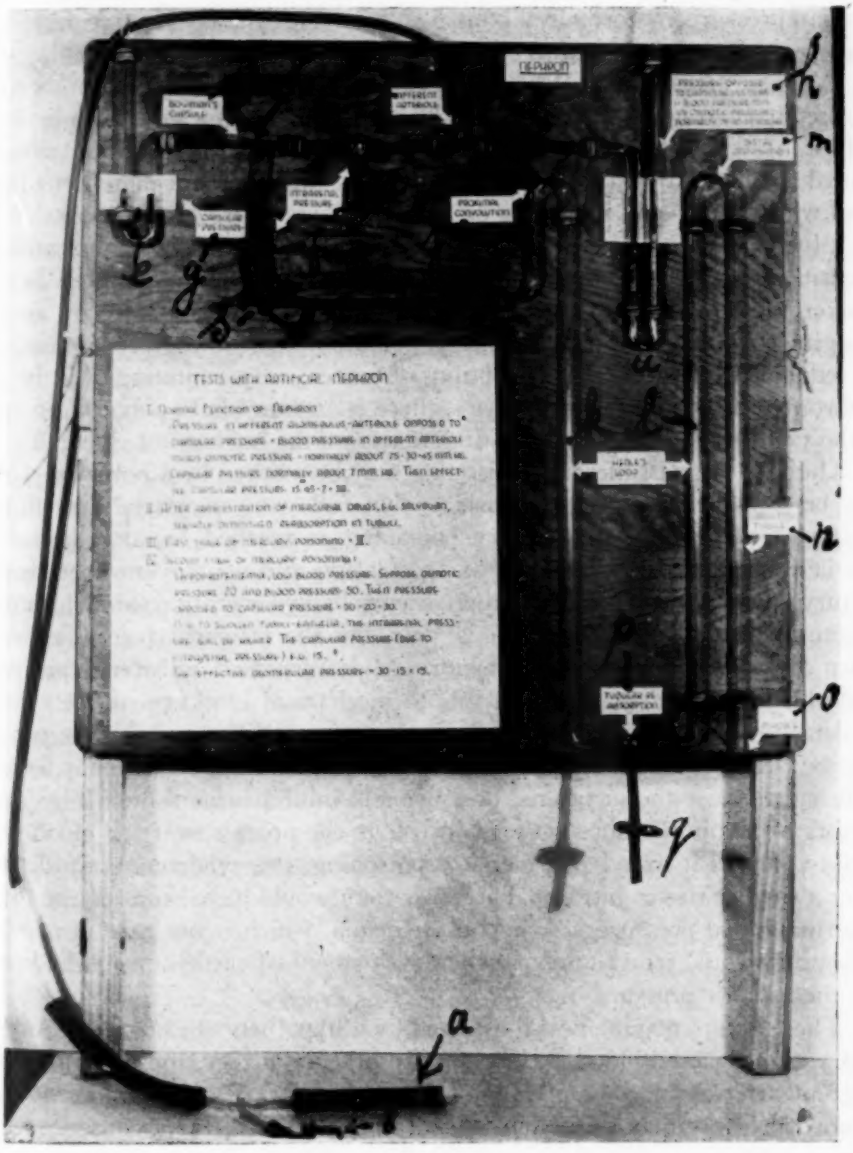

FIG. 1. Artificial nephron. See description in text.

Normal Intratubular Pressures. The following figures are estimations for man and are deduced from measurements made on isolated blood-perfused kidneys of dogs (Winton [1]). With a normal blood pressure in the brachial artery, the blood pressure in the afferent arteriole is about 75 mm.

Hg. The osmotic pressure in this vessel is normally about 30 mm. Hg. The difference, indicating the pressure opposed to the pressure in Bowman's capsule ("capsular pressure") is, therefore, 75–30, or 45 mm. Hg. The capsular pressure is normally about 5–7 mm. Hg. The effective filtration pressure or actual driving force will, therefore, be 45–5 or 40 mm. Hg.

"Normal" Function. When the pressures in the artificial nephron were adjusted to correspond to these normal figures, there was a slow drop-by-drop outflow of water representing the urine from the collecting tubule passing toward the bladder (figure 1, 0) and another outflow from that part of the tubes which represents the places of reabsorption (figure 1, p. 223).

"Abnormal" Function. Examples of abnormal function are imitated by a consideration of the diuretic action of mercurials. Blumgart [2] in 1934 and Walker [3] in 1937 found that salyrgan causes a diuresis in spite of an unchanging rate of glomerular filtration. This mercurial, therefore, must act by reducing the tubular reabsorption of water. By imitating this in the nephron with the aid of a clamp (q), there is an immediate polyuria, in spite of the fact that the rate of supply of water from the tap has not changed.

The first stage of mercury poisoning may be marked by a polyuria, which may be explained on the same basis as that following mercurial diuretics.

The second stage of mercury poisoning is marked by an oliguria or anuria which has been a matter of speculation and controversy for over a century. In mercury poisoning there are probably several factors which contribute to produce the oliguria or anuria, but the principal factor, as in all other diseases which show the syndrome, is increased intrarenal pressure. The old theory which attributed this to mechanical blockage of the tubules by detached necrotic cells is entirely inadequate. Within a week the tubules may be clear of detritus, yet show a degree of dilatation which is apparently sufficient to raise the intrarenal pressure and inhibit urine flow. Two other factors of less importance may play a rôle in the process. If the blood pressure is low, as it may be in mercury poisoning, the syndrome may develop after a smaller rise in intrarenal pressure than would have been required with a normal blood pressure. A hypoproteinemia, which is not rare in mercury poisoning, would tend to prevent the development of the syndrome by lowering the osmotic pressure.

These points may be best illustrated by a hypothetical example. Assume that with a lowered blood pressure in the brachial artery, the pressure in the afferent arteriole may be 50 mm. Hg (instead of about 75 mm.) and the osmotic pressure may be 20 (instead of about 30 mm.) as a consequence of hypoproteinemia. The difference, 50–20, or 30 mm. Hg, indicates the pressure opposed to the capsular pressure. The latter, as a result of the increased intrarenal pressure, may be 25 mm. Hg (instead of the normal 5–7). If the pressures in the artificial nephron are so adjusted that the manometers read 30 and 25, respectively, the "polyuria" disappears and is replaced by "oliguria" and later by anuria. The same happens if the blood pressure in

the afferent artery is normal, provided the intrarenal pressure is sufficiently increased.

If the pressures in the apparatus are so adjusted that the effective filtration pressure is near the critical level, a rise or fall of a few mm. of Hg in the intrarenal pressure will result in "anuria" on the one hand, or a free flow of fluid on the other. This "anuria" appears without the introduction of any obstruction in the tubules, such as might be imitated by the application of a clamp to one of the tubes. It is exclusively the result of an increased intrarenal pressure.

Pathological Findings. In all cases of the syndrome a high tension of the renal capsule is probably present. This may be demonstrated at autopsy provided the latter is carried out very shortly after death, before rigor mortis has set in. Morrison [4] has reported three cases of crush injury which came to autopsy before rigor mortis, in all of which the cut edges of the kidney bulged out over the capsule. The same observation was made in the case reported by the author, and illustrated in figure 3.

The pathological lesions in the kidney which may cause the increased intrarenal pressure, have already been mentioned. In the case of crush injury (and probably in some other diseases) the swelling of the tubular epithelium is probably caused by some toxic substance ("nephrotoxin") liberated by the damaged tissues.

Brief reports of five patients who died with the syndrome follow, together with illustrations showing the pathological lesions in the kidneys. With the exception of the case of crush injury which occurred in California, all the cases came to autopsy in the Charity Hospital of Louisiana at New Orleans. Most of these show that the tubules are more or less displaced either by an interstitial edema with or without signs of inflammation or by neoplastic tissue. Some sections show only swelling of the tubular epithelium. In some cases, however, other sections of the same kidney may show interstitial edema. Occlusion of tubules by blood clots or cell detritus may be completely absent in cases dying of the syndrome.

Figure 2 is a kidney section of a patient 35 years of age who became suddenly ill on October 14, 1944 with high fever and malaise and who died seven days later in uremia. No pyogenic infection was found during life or at postmortem examination. No definite diagnosis could be made, even at autopsy, except that it was probably a virus infection. A cause for the oliguria and anuria which preceded the uremia and for the uremia itself was not found. The lungs showed an interstitial pneumonitis with the well-known hyaline membrane, lining the alveoli. The author could not find a description of a similar alveolar lining in other virus infections than the fulminant form of influenza. In these forms of influenza which the author also saw in Holland in 1918, there is often an abundance of inflammatory edema, not only in the lungs (interstitial pneumonitis) but also in other organs. In this case it was present in the kidneys (interstitial nephritis), undoubtedly

causing an increase of the intrarenal pressure sufficient to produce the syndrome.

Figure 3 represents the picture of a kidney section of a patient who died from crush injury in November 1944 as victim of an airplane crash in Cali-

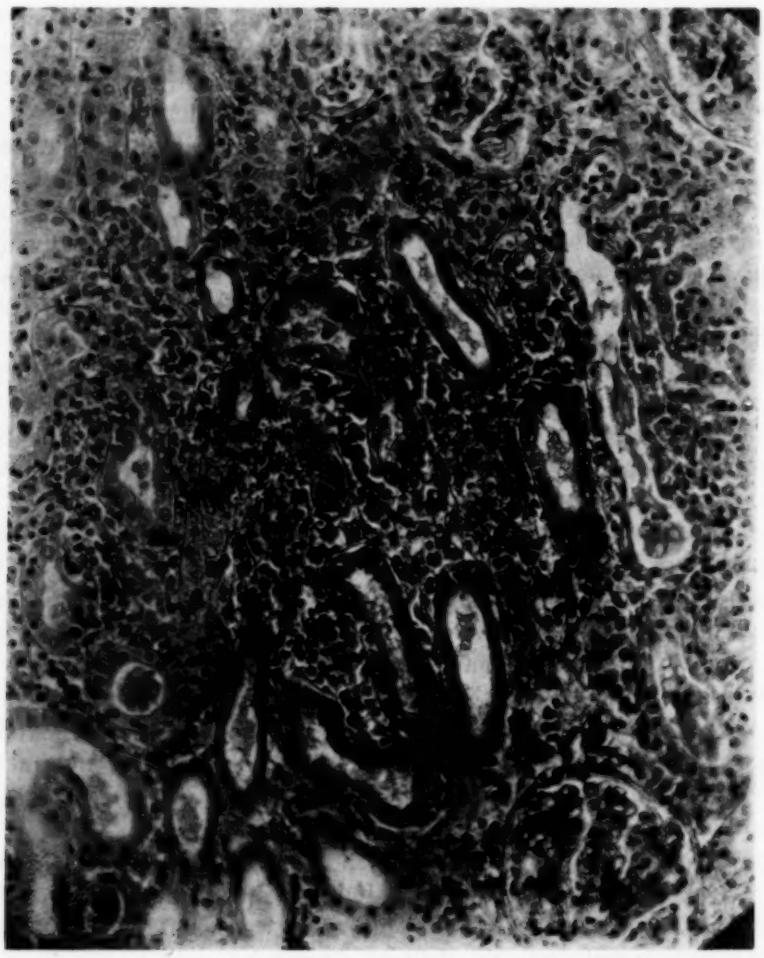

FIG. 2. Kidney section of a case which showed the syndrome, in consequence of an interstitial nephritis (part of a fulminant form of influenza). Notice the inflammatory edema, considered the cause of an increased intrarenal pressure, in the interstitial tissue. There were no true obstructions of the tubules, which proves that obstructions may be completely absent in anuria.

fornia. His left leg was squeezed in the remnants of the airplane for five hours. The autopsy report stated: "On section of the kidney the cut edge everts and the cortex is raised above the surface of the capsule, as well as the medulla and pyramids." Figure 3 shows the enormous swelling of the tubular epithelium, but according to the report there was also found edema of

the interstitial tissue about the collecting tubules. The picture corresponds completely with the description by British pathologists of such cases of crush injury before the new treatment was applied.

Figure 4 represents a kidney section of a patient, a white female 40 years of age, who had lymphomatosis (Kundrat's lymphosarcoma). Lymphomata were found in many organs, including the renal interstitial tissue. The

FIG. 3. Kidney section of a case which showed the syndrome, in consequence of a crush injury (airplane crash). Notice the intense swelling of the tubular epithelial cells. This swelling is considered the cause of an increased intrarenal pressure.

tubules were displaced by lymphomatous tissue. The patient showed an oliguria and a non-protein nitrogen of 235. After three weeks she died from pressure anuria. This demonstrates that neoplasms may cause the syndrome, if their presence between the tubules causes increased intrarenal pressure, without any significant damage to the tubular epithelium or glomeruli and without interstitial edema.

Figure 5 represents a section of the kidney from a patient who committed suicide with mercuric chloride. The principal features are described in the legend.

Figure 6 represents a section of the kidney of a patient who died following a transfusion of incompatible blood. The old explanation which attributed the anuria to the blood casts has already been rejected by many pathologists because these casts are often negligible in amount in fatal cases. Boyd [5] stated: "It seems probable that there is some other explanation." The most important features are described in the legend.

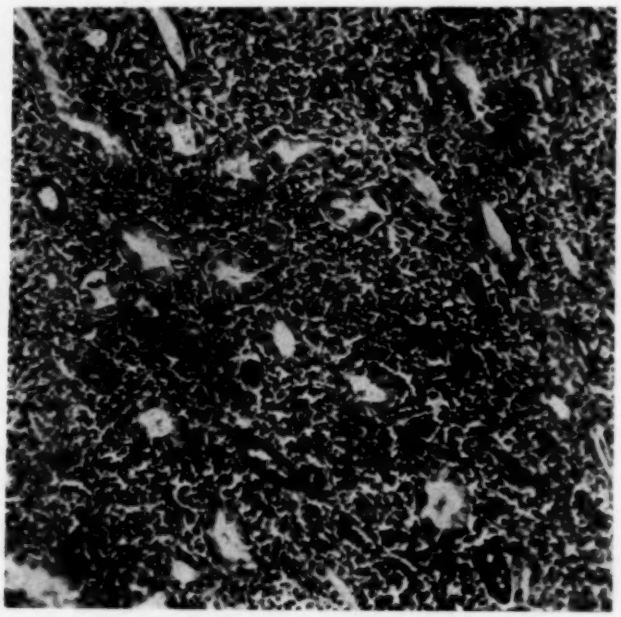

FIG. 4. Kidney section of a case which showed the syndrome, in consequence of lymphosarcomatous tissue in the renal interstices which is considered the cause of an increased intrarenal pressure. No cellular swelling or obstructions.

Differential Diagnosis. The "malignant pressure oliguria" which constitutes a part of the syndrome under discussion must be differentiated from a "benign pressure oliguria" which is caused by renal stasis, e.g., in heart failure. The latter does not lead to pressure uremia, as far as we know at the present time. Various explanations, none of them satisfactory, have been offered for the oliguria of congestive failure, including increased colloidal pressure in the blood vessels, an alteration of the permeability of the invaginated part of Bowman's capsule, as a result of anoxia, and slowing of the circulation through the glomeruli. Although one or more of these factors may contribute to the oliguria, the main cause, the writer believes, is an increase of the intrarenal pressure caused by the dilatation of the veins. This oliguria may be called "benign" because it is reversible spontaneously or

under the influence of digitalis or diuretics. With disappearance of general venous stasis the intrarenal pressure decreases to a normal level and normal urine flow is restored.

FIG. 5. Kidney section of a case which showed the syndrome, in consequence of mercury poisoning. Notice the dilatations of the tubules by detritus of blood and desquamated cells, with here and there precipitates of calcium, or dilatation without detritus caused by obstruction in lower parts of the tubules. These dilatations of the tubules are considered the cause of an increased intrarenal pressure. (Such obstructions are only present in parts of the kidney and therefore *completely insufficient* to explain the anuria.)

To differentiate pressure uremia from the uremia of glomerular nephritis is usually not difficult unless both are present in the same patient. The typical picture of the syndrome, the history and the clinical evidence of a disease [30] which may cause it, will usually be sufficient to exclude a glomerular uremia. The blood pressure is too variable to be of value. The usual renal function

tests are also unreliable, because they can not detect beginning renal injury during oliguria. Study is in progress regarding a renal function test which is reliable in cases of oliguria and which is easier than the Iodo-secretory Index, the results of which are also reliable in oliguria (Peters [6]).

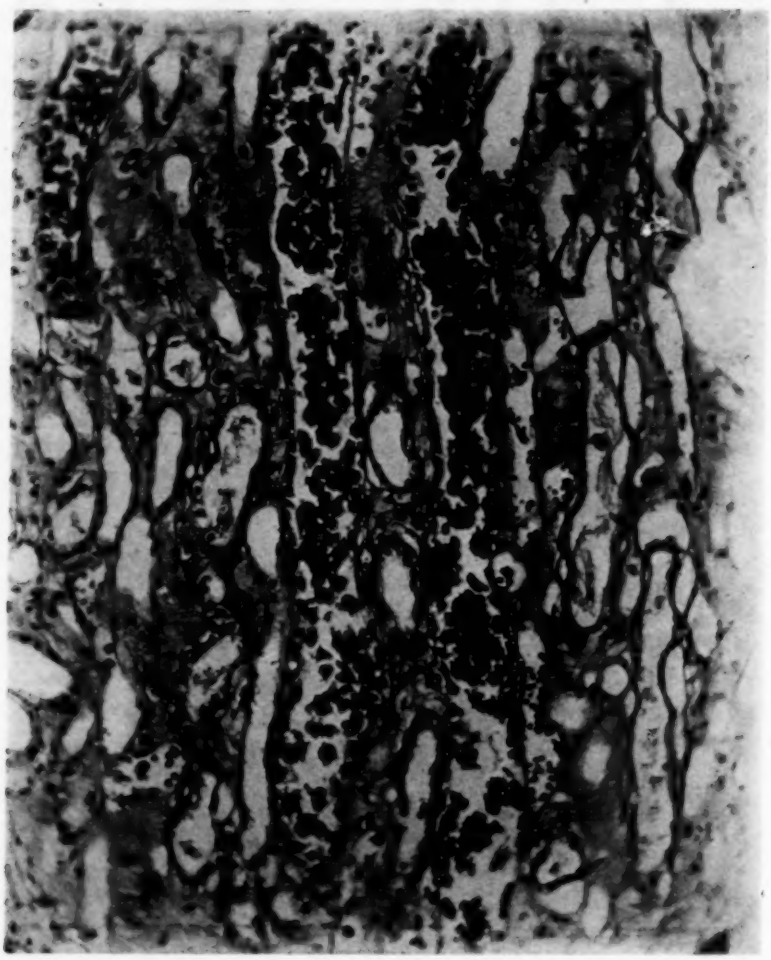

FIG. 6. Kidney section of a case which showed the syndrome, in consequence of a blood transfusion (incompatibility). Notice the dilatations of tubules by detritus of blood and desquamated cells. These dilatations and additional dilatations above the points of obstruction are considered the cause of an increased intrarenal pressure. (Such obstructions are present only in a part of the kidney and therefore *completely insufficient* to explain the anuria.)

In the next part of this article only the Transfusion Kidney, the Crush Injury and their therapy will be discussed.

Transfusion Kidney. This name includes, by definition, the disease syndrome which may follow a mismatched blood transfusion. The symptoms

of Transfusion Kidney need no description here. Bordley [7] described an interesting series of 17 cases, in all of which suppression of urine was the outstanding feature, always associated with hyperazotemia. Of this group of patients 11 died and six recovered: a mortality rate of 65 per cent. Navasquez [8] writes, in 1940, that he disagrees with all the explanations of the oliguria or anuria which he found in the literature and he adds that further investigations are desirable.

Crush Injury. During the Messina earthquake of 1908 many of the 65,000 dead died from Crush Injury, as may be concluded from an article written by Colmers,[9] head of a Relief Expedition. In 1916 Frankenthal described the symptoms of Crush Injury in soldiers during the first World War. It was the result of a mine explosion. In March 1941 Bywaters and Beall [10] published the first paper about Crush Injury, observed during the terrible bombardments of London, about September 13, 1940. They call it erroneously "a hitherto unreported syndrome." About 5 per cent of all casualties during large air raids in urban areas appear to be Crush Injuries. The flying bomb, especially the noiseless type, has increased its number. The symptoms need no extensive description here. On admission to the hospital the patient who has usually been buried for several hours, with pressure on a limb, appears in good condition, except for swelling of that limb. However, there is often (not always) present a "pre-shock period" which may be discovered by the presence of a hemoconcentration, preceding the fall of the blood pressure. The hemoconcentration may reach figures of 22 grams per cent hemoglobin, corresponding to a plasma volume of about one liter. If the symptoms of shock disappear with or without therapy, one often observes the symptoms of the syndrome. These symptoms are independent of the precedent shock, because cases of Crush Injury are described without shock. Morison [4] described three such cases without shock, all three with fatal result. Most of the victims were buried under debris between three and 12 hours. The existence of a nephrotoxin, formed in the crushed muscles, seems to be admitted by most of the investigators. In dogs whose limbs were crushed, mitochondrial changes are found in the tubular epithelial cells, suggesting the action of a nephrotoxin (Eggleton et al.[11, 12]).

Prognosis. Bywaters [13-14] in 1942 stated: "About one-third of the patients with crush injury have recovered, but these were only minor cases without severe shock or without uremia." From this statement one may conclude that nearly all patients with a fully developed crush injury, including uremia, will die. This is in accordance with the observations of Broster and of Patey. Broster,[15] in 1943, wrote regarding the therapy of crush injury: "There is not much that can be done" and "Few survive when the syndrome is marked." Patey [16] wrote: "Most surgeons have had the distressing experience of seeing their patients (with crush injury) pass from a good general condition to death from anuria, despite heroic measures to re-establish the urine flow."

Treatment. In all diseases associated with this syndrome an attempt should be made as soon as possible to decrease the high intrarenal pressure which is the cause of the anuria or oliguria.

Of the older methods of treatment, the following are contraindicated because they are positively or potentially injurious. 1. Administration of large amounts of fluid. 2. Protein starvation. 3. Massive doses of protein. 4. Intermittent pressure on the crushed limb. 5. Injections of salyrgan. 6. Injections of adrenal cortical extract.

The administration of large amounts of fluid has been extensively employed, without benefit. For example, Younge [17] described a case of transfusion kidney in which the daily urinary output remained between 50 and 100 c.c. in spite of daily injections of three liters of 2.5 to 10 per cent glucose solution. Dunn [18] described the case of a girl of 18 who developed the symptoms of crush injury after being pinned under a beam for six hours during an air raid. In spite of a fluid intake of about 3600 c.c. per day, the urine output was only about 250 c.c., and she died after a few days in uremia. The author observed a white woman, 43, who developed anuria and died in uremia in spite of the administration of not less than seven liters of fluid a day. The autopsy revealed an interstitial nephritis with marked edema of the renal interstitial tissue. One may assume that the administration of excessive volume of fluid tends to build up or increase a renal interstitial edema, and thus hampers recovery. Wakeman [19] observed the syndrome in several cases of blackwater fever in West Africa. Later in this country he observed a case in a girl of 20 who had taken large doses of quinine. After her condition had become critical and the non-protein nitrogen had risen to 237 mg. per cent, he stopped all fluids, and she immediately improved and finally recovered. Although this may have been purely a coincidence, the observation should be kept in mind. The author many years ago pointed out the danger of injections of large amounts of fluid in oliguria or anuria. Styron and Leadbetter [20] in 1944 stated: "A frequent mistake in the therapy (of anuria) is the aimless administration of intravenous fluid."

The administration of alkali in cases of transfusion reaction was recommended by Baker and Dodds [21] in 1925, with the object of preventing the deposition of acid hematin in the renal tubules in cases of transfusion reaction. It is now known that obstruction of the tubules with hematin is not essential for the development of the syndrome, since fatal cases of transfusion reaction have been reported without hemoglobinuria (Bancroft [22]) and with persistently alkaline urine without alkali administration (Navasquez [8]). The alkalinization of the urine is apparently harmless but superfluous.

The treatment recommended consists of: 1. Bilateral decapsulation of the kidneys. 2. Restriction of fluid intake. 3. Administration of certain diuretics. 4. Administration of drugs to raise blood pressure, if the latter

is low. These measures should be carried out early, as soon as the syndrome is diagnosed.

1. Bilateral decapsulation. In experiments on animals it has been shown that this procedure reduced the intrarenal pressure by about 50 per cent. There is no good reason to suppose that this would be less in the human being. This would probably be more than enough to abolish the oliguria in man.

Decapsulation was first performed by Harrison (1896). Edebohl (1901) reported the successful use of the procedure in 18 cases, without a death (according to Da Costa [23]). Among others who have used and recommended decapsulation in cases of acute or chronic nephritis with anuria, may be mentioned Talma (1908), Bessesen [24] (1924), Warbasse and Smyth,[25] and Bickham.[26] All of these used it only as a last resort measure, after the usual conservative measures had failed and the patient was in a highly critical condition. The fact that successful results were obtained, even under such unfavorable conditions, would indicate that bilateral decapsulation is not a dangerous operative procedure.

Bancroft [22] was probably the first who performed a decapsulation in transfusion kidney (1925), but he had used "every therapeutic aid that he knew of, before performing this surgical intervention." On the eighth day of oliguria (30 c.c. urine per day) the blood urea nitrogen was 64 mg. per cent, the serum calcium was 4.8 mg. per cent, and tetany was present. He did the decapsulation on the ninth day when the patient was in extremis. Immediate relief followed, and the patient recovered completely. Another successful case was reported by Young [17] in a woman of 33 after a transfusion reaction, also as a last resort measure. He described the capsule as extremely tense.

Talbott [27] studied the effect of unilateral decapsulation on the fourth day of anuria in a woman suffering from a transfusion kidney. Catheters were inserted in both ureters. Urine flow was established 24 hours later. As there was no difference between the urine volumes from the two kidneys and as there was no striking difference in the function of the two kidneys, tested separately six weeks later, he interpreted this "as implying that unilateral decapsulation had no beneficial action on renal function." It seems possible, however, that the operation did cause a resumption of urine flow in the decapsulated kidney, and that this was soon sufficient to cause a little decrease of the interstitial edema and intrarenal pressure in the other kidney.

The writer believes both kidneys should be decapsulated as soon as the syndrome can be established, by the presence of oliguria (or anuria) and hyperazotemia. It should not be used merely as a last resort measure. If done promptly, the risk of operation is much less, and unnecessary damage to the kidneys and other organs can be avoided.

The reasons for restriction of fluid intake have been discussed. It is probable that burdensome restriction is unnecessary and that enough fluid may be allowed to satisfy thirst.

Most of the diuretics have been tried without success. Henderson,[28] however, has reported recovery of a case of crush injury following the intravenous injection of isotonic solution of sodium sulfate. It seems possible that its action may have been due to drawing fluid from the interstitial tissue into the tubules by its osmotic pressure. Although this result may have been accidental, it seems worthy of further trial, especially with slight hypertonic solutions.

The administration of caffein and coramine is recommended to raise the blood pressure in cases with hypotension. This will help to counteract the effect of the increased intrarenal pressure.

As a means of preventing the development of the crush syndrome, Patey's suggestion[29] to bandage the crushed limb immediately after liberation deserves consideration. By loosening the bandages very slowly after the patient is transferred to a hospital, a *gradual* restoration of the circulation through the crushed tissue will take place and the "nephrotoxin" consequently will reach the kidneys in lower concentration. This is supported by two observations. First, Eggleton et al.[11-12] found that in experiments on cats with crushed limbs, the creatinine tolerance remained normal if the circulation were readmitted slowly, whereas it was decreased if this were done abruptly. Second, it was observed that in patients who were buried longer than 12 hours, the syndrome often did not appear, probably because the circulation could not be restored quickly.

Summary

1. A syndrome consisting of oliguria or anuria, hyperazotemia and uremia, with a high mortality rate, is described.

2. The syndrome may be present in many different diseases.[30]

3. The primary cause of the oliguria or anuria is a decrease of the effective filtration pressure as a result of an increased intrarenal pressure.

4. The intrarenal pressure can be increased by dilatation of part of the tubules, by interstitial edema, by inflammatory exudate, by swelling of the tubular epithelial cells, by interstitial neoplasms, etc. Dilatation of a part of the tubules may be caused by obstructions, either at or below the areas of dilatation. The obstructing substances may be detritus of tubular epithelial cells or of blood cells, crystals, or certain types of casts. Swelling of the cells, interstitial edema or exudate presumably can be produced by toxic substances which may develop within the body or be introduced.

5. Experiments with an artificial nephron demonstrate that an increase of a few mm. Hg, in the intrarenal pressure, may cause "oliguria" or "anuria." A slight reduction of an increased intrarenal pressure (which can easily be obtained in vivo by decapsulation) promptly restores the normal "urinary output." It is estimated from animal experiments that bilateral decapsulation decreases the intrarenal pressure by about 50 per cent, which is undoubtedly more than sufficient to restore a normal urinary output.

6. The therapy previously employed did not reduce the mortality rate of a fully developed syndrome below nearly 100 per cent in crush injury, below 65 per cent in transfusion kidney, or below 60 per cent in many of the other diseases associated with the syndrome. This old therapy, founded on wrong conceptions as to the etiology, probably often hampers recovery by producing or increasing interstitial renal edema.

7. The therapy proposed for the syndrome in any disease in which it occurs, should be instituted immediately after it appears. It consists of one or more of the following procedures: 1. Emergency bilateral decapsulation. 2. Restriction of fluid intake. 3. Administration of certain suitable diuretics. 4. Administration of drugs which raise the blood pressure in cases with low blood pressure. In severe cases all four procedures may be necessary.

8. An emergency decapsulation in severe cases associated with the syndrome, is more urgent than an appendectomy in acute appendicitis because the average mortality is much higher in the former than in the latter. A decapsulation will seldom do harm, in the hands of a competent surgeon.

9. Diseases associated with the syndrome should be admitted as emergency cases on a surgical ward.

The following quotation is from a letter from one of the Editors of *The Lancet*, who read the article sent by the author to the Medical Staff of the British Army in June 1944.

"You are no doubt right in urging that the raised intrarenal pressure is the basis of the transfusion and crush kidney, and that this can best be treated by decapsulation. The treatments which you recommend—decapsulation, diuretics, and pressor drugs—are now widely used, separately or in combination."

The author would appreciate receiving short reports of cases treated by this method.

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30. Thirty-four diseases, in which the syndrome may appear, are mentioned in an article that will be published in the Acta Medica Scandinavica (Stockholm), in the near future. More extensive discussion about these diseases, with quotation of examples, will be published later.

CASE REPORTS

THROMBOCYTOPENIC PURPURA FOLLOWING THE USE OF SULFATHIAZOLE *

By Paul S. Strong, Major, M.C., and Edward M. Glassburn, Captain, M.C.

Thrombocytopenic purpura following the use of the sulfonamides is a rare but serious complication. In some instances it appears to be the result of an acquired sensitivity to the drug, whereas in others it represents a true idiosyncrasy and may follow the initial experience with the sulfonamide. Werner [1] reported a case of thrombocytopenia which appeared after the administration of only 1 gram of sulfathiazole. This patient had a history of having received the same drug 20 days before without reaction. Toxic thrombocytopenia was described by Goldbloom et al.[2] in a 50 year old female who had received only 6 grams of sulfapyridine. Hurd and Jacox [3] recently reviewed the literature on the subject of thrombocytopenia following the sulfonamides and added two more cases. When the platelet count of their sulfathiazole-sensitive patient had returned to normal, they retested him with sulfathiazole and sulfadiazine and noted the same type of toxic reaction with both drugs.

This report is not submitted merely to add another case history to the literature but rather to relate the therapeutic dilemma which developed when a sulfathiazole sensitive patient developed almost all of the known complications of scarlet fever.

Case Report

A white soldier, aged 19, was admitted to the Station Hospital on March 16, 1943, because of "a breaking out" on his body which he had first noted that morning. He had no other complaints and was anxious to return to duty. On physical examination the temperature, the pulse, and the respirations were normal. There was a widespread maculopapular rash on the face, neck, trunk, and extremities. The occipital and posterior cervical lymph nodes were enlarged. There were no Koplik spots visible in the mouth. A diagnosis of German measles was made and general supportive treatment was given. The rash gradually faded and the patient seemed perfectly well.

On the seventh hospital day, the temperature, which had been consistently normal, suddenly rose to 101° F., and a punctate erythematous rash became apparent on the patient's chest. At the same time, the patient began to complain of severe sort throat. The pharynx was acutely inflamed and the tonsils were covered partially by a grayish yellow exudate. Circumoral pallor was present and a typical strawberry tongue was seen. A diagnosis of scarlet fever was made and treatment was instituted. Because of the follicular tonsillitis, oral administration of sulfathiazole in divided doses was started. No history of previous sulfonamide therapy was obtained. After 19 grams had been given over a three day period, the drug was stopped.

* Received for publication March 6, 1944.

The day after the sulfathiazole was discontinued the patient began to bleed from his nose. This bleeding continued for four days. All conservative local and systemic measures were tried with but moderate success. The bleeding points were multiple, confined to the left nasal passage, and rapidly filled that cavity with a pulsating well of blood. However, the bleeding could be controlled with iced saline irrigations allowing adrenalin saturated packs to be inserted. Abnormal pulsation of the angular, temporal, and carotid arteries gave evidence of the vascular tension of the head and neck and partially explains why the tightly inserted nasal packs were gradually extruded by the pulsating blood clots.

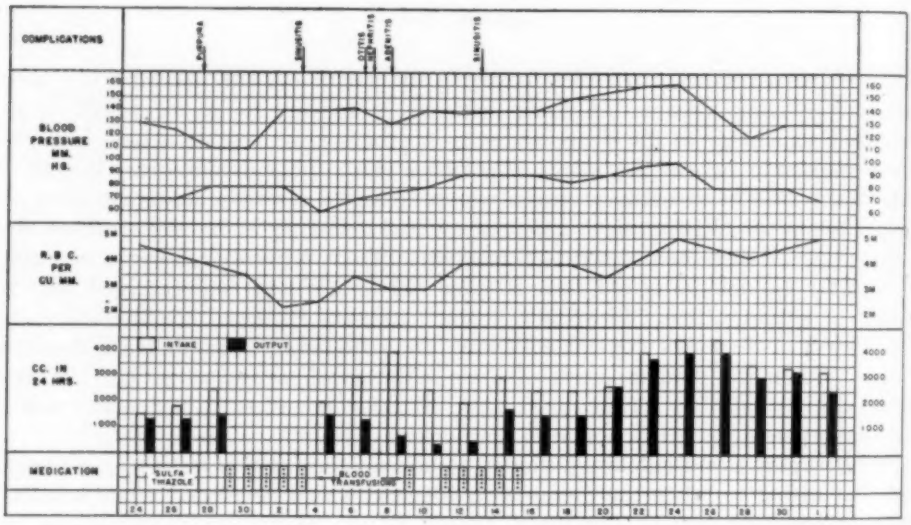

FIG. 1.

The second day of nasal bleeding a widespread petechial and ecchymotic rash appeared on the skin and mucous membranes. With continued hemorrhage the purpuric spots were seen on the gums, fauces, over the sacrum, about the elbows, and at other pressure points. At this time the red blood cell count was 2,630,000 per cu. mm., the hemoglobin was 9.8 grams per 100 c.c., the platelet count was 166,000 per cu. mm. and the white blood cell count was 25,350 per cu. mm. The Rumpel-Leed test was positive. The urine was negative. The blood Kahn reaction was negative. In spite of four days of intensive treatment with small (250 c.c.) blood transfusions, vitamin K, vitamin C, and calcium subcarbonate, the hemorrhagic tendency increased as evidenced by the presence of blood in the urine and stools. A second platelet count done two days after the first, showed 100,000 platelets per cu.mm. Although the bleeding time was longer than 15 minutes, the clotting time was normal.

After five days of persistent bleeding, the hemorrhagic tendency disappeared abruptly and the patient's general condition improved markedly. With the exception of the appearance of a purulent rhino-sinusitis, the next three days were uneventful. On the fourth day the patient's temperature became elevated and he complained of pain in his right ear. Conservative aural treatment was begun but on the following day a myringotomy under local anesthesia was performed because of increased pain and bulging of the drum. A hemolytic streptococcus was isolated from the aural discharge but the risk of further bleeding did not justify the use of chemotherapy.

Coincident with the development of the otitis media, a marked bilateral anterior and posterior cervical lymphadenitis was noted.

The patient's course was further complicated by the development of the signs and symptoms of an acute glomerulonephritis. This was manifested by puffiness of the hands and face, diminished urinary output, marked pallor, elevated non-protein nitrogen and by the appearance of albumin, red blood cells, and casts in the urine. Coincident with the onset of all these complications the patient's condition became critical. For the next three days the pharyngeal airway became progressively decreased owing to the external pressure of the greatly enlarged cervical glands and the respiratory difficulty was further increased by a definite air hunger resulting from the marked anemia. Small blood transfusions and intravenous injections of 10 per cent glucose solution were given as supportive treatment with slow but progressive improvement. The dyspnea disappeared with the subsidence of the cervical adenitis, the urinary output increased, the edema cleared, and the aural and postnasal discharges diminished. However, with this general improvement, a definite hypertension developed which was accompanied by a persistently elevated sedimentation rate and albuminuria. The Mosenthal and phenolsulfonphthalein tests demonstrated impaired kidney function although the non-protein nitrogen was normal.

Within the next four weeks all signs of nephritis disappeared. The urine cleared completely, and the blood pressure, the sedimentation rate, the phenolsulfonphthalein and the Mosenthal tests were all within normal limits.

After one month of sick furlough, the patient returned to full military duty. A follow-up made six months later showed the patient to be in good physical condition.

Comment

Considerable variations occur in the enumeration of blood platelets owing to their tendency to clump and to certain other mechanical difficulties. Values below 200,000 per cu. mm. are generally considered to be less than average, whereas counts of less than 130,000 denote a pathological deficiency. The second platelet count of 100,000 per cu. mm. obtained in this case, together with the prolonged bleeding time, the normal clotting time and the poorly retracting clot were believed sufficient evidence to classify this purpura as one belonging in the thrombocytopenic group.

It has seemed feasible to us to assume that the thrombocytopenia was due to sulfathiazole. Whether the general toxicity of the hemolytic streptococcic infection was a significant additional factor in the causation of this condition cannot be positively stated. The Dicks [4] fail to mention thrombocytopenia as a complication of scarlet fever in their book, although there are a few reports in the literature of purpura following the malignant forms of smallpox, diphtheria, scarlet fever and other streptococcal infections.

Hemorrhage into the gastrointestinal tract and kidneys is a frequent finding in purpura. In some instances a true nephritis is simulated by the hematuria, albuminuria, and the depression of renal function. In the case presented the initial hematuria associated with the other hemorrhagic manifestations was thought to be an example of this pseudo-nephritis. The secondary hematuria occurring nine days later, after two negative urinalyses had been obtained, was considered to be a true post-scarlatinal nephritis.

Although it was desirable to retest this patient with sulfathiazole after his recovery, the severity of his reaction and the nearly fatal outcome did not justify this procedure.

SUMMARY

A case of scarlet fever with thrombocytopenic purpura and severe hemorrhagic manifestations which developed following the administration of 19 grams of sulfathiazole by mouth during a three day period is reported. The extreme difficulty which was encountered in controlling the hemorrhagic manifestations is emphasized. The therapeutic impasse that was reached when, following the control of the hemorrhage, the patient developed suppurative otitis media, marked cervical lymphadenitis, severe sinusitis, and nephritis is mentioned. Multiple transfusions, local treatment and general supportive measures proved to be life saving in this instance.

The authors wish to express their indebtedness to Capt. Harry Levitt, M.C. and to various members of the Surgical Service of the Station Hospital for their part in saving this soldier's life.

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PROGRESSIVE (DISSEMINATED) COCCIDIOIDOMYCOSIS: REPORT OF A CASE*

By CHARLES D. MARPLE, Capt., M.C., A.U.S., *Santa Ana, California*

COCCIDIOIDOMYCOSIS, which is still occasionally and erroneously referred to as a "tropical disease," is an infection caused by the fungus *Coccidioides immitis* (Rixford and Gilchrist, 1896) and occurs endemically in the San Joaquin Valley of California and over large areas in the Southwest. The disease, both in its benign primary form and in the fortunately uncommon disseminated form, has become thoroughly familiar to military medical officers stationed in these areas during the present war. It is reasonable to believe that physicians in other regions of the United States will encounter occasional cases of coccidioidomycosis when men who have been stationed previously in the endemic areas return to their homes. For this reason even single case reports of disseminated coccidioidomycosis would seem worth publishing. This particular case is presented because of the rather complete observation of the clinical and laboratory course of the disease, because of the futile but somewhat suggestive treatment with coccidioidin vaccine and because of the unusual occurrence of paraplegia secondary to an extradural coccidioidal abscess.

The terms "progressive coccidioidomycosis" and "disseminated coccidioidomycosis" are synonymous with the older and less appropriate titles of "coc-

* Received for publication March 31, 1944.
From the Medical Department of the California State Prison, San Quentin, California.

cidioidal granuloma" and "secondary, or chronic coccidioidomycosis" and are applied to the progressive, highly fatal form of the disease. The ratio of the incidence of this form of the disease to that of the frequently subclinical and ordinarily benign "primary coccidioidomycosis" is no greater than 1:500. For a discussion of nomenclature and for an excellent summary of our present knowledge of coccidioidomycosis, the reader is referred to the recent review by C. E. Smith.[1]

Case Report

A 36 year old negro male entered the Charles Neumiller Hospital on April 15, 1941 because of "pain in the right foot" of one month's duration. His family history was not contributory. He denied any known contact with tuberculosis. He had been born in Texas and had lived there for 19 years. For five years he had been a porter on railroads operating between Los Angeles and Salt Lake City, and he had resided in Los Angeles between trips. From 1930 until 1937 he had served a prison sentence in the California State Prison at San Quentin. For nearly three years he had performed day labor on a ranch in Monterey County on the coast of California. From June 1940 until February 1941 he had lived in San Francisco. He denied ever having been a resident of the San Joaquin Valley.

The patient had had syphilis, first manifested by a chancre and positive blood serologic reaction in 1930 for which he had been treated with 15 injections of neoarsphenamine and 30 injections of a bismuth salt. Treatment had been discontinued after repeatedly negative blood and spinal fluid serological tests had been obtained. In 1932 his spinal fluid had exhibited a negative Wassermann reaction, a normal protein content and a colloidal gold curve of 5544331000. There had been several unrelated accidents, operations, and minor illnesses. Review of the body by systems elicited no complaints prior to the onset of the presenting illness.

The present illness had begun with an attack of "the flu" about two months previously. This had consisted of chills and fever, generalized aches and pains, a moderately productive cough and a rapid and considerable weight loss over a short period of time. A fortnight later the patient had first noted the spontaneous occurrence of pain over the instep of the right foot. This pain had become progressively more severe and had radiated up the front of the lower leg. There was no history of trauma to the foot. At about the same time there had appeared on the bridge of his nose a painless erythematous swelling which had gradually increased in size. This swelling had been incised by a physician and had drained small amounts of pus persistently thereafter. A similar swelling had appeared on the radial side of the right forearm just above the wrist, had ruptured spontaneously and had exuded purulent material intermittently. Other swellings had appeared subsequently on both thighs, behind the left knee, on both upper arms, on the dorsum of the left hand and on the right side of the forehead. These swellings had grown in size and some had assumed a dusky red hue. There had been a weight loss in excess of 20 pounds in two months.

Physical examination revealed an emaciated negro male in no discomfort. Pupils were dilated and equal; the right pupil reacted to light, the left did not. There was a small subcutaneous abscess on the right side of the forehead. A similar but smaller abscess was present just above the inner canthus of the right eye. On the bridge of the nose was an erythematous swelling with a central eschar from which pus could be expressed. No abscesses were present on the neck or the trunk. Breath sounds were diminished at the right lung base posteriorly where dry râles could be heard. Cardiovascular examination was completely normal. No abdominal organs or masses could be felt. There were no enlarged lymph nodes. Reflexes were physiological and

equal throughout. There were several superficial abscesses on each thigh and one behind the left knee. There was a draining abscess above the right wrist and multiple fluctuant swellings on both upper arms. On the dorsum of the right foot was a tender, diffuse and slightly discolored swelling. There were numerous small and large traumatic scars on various portions of the body.

The results of the initial and subsequent laboratory studies are summarized in table 1. Skin tests with tuberculin (0.1 c.c. 1:10,000 dilution) and with coccidioidin

TABLE I

Laboratory Record

Date	Blood							Miscellaneous Laboratory Findings
	RBC (mil.)	Hgb %	WBC	PN	LY	Eos./ Baso.	Sed. Rate	
4/15	4.92	64	15,200	78	16	3/1	30	Urine: Pus cells 5–7/HPF; Alb. Tr.
19								Blood Wa. R. and Kahn doubtful positive
23								5 sputa negative for tuberculosis
24								*Cocc. immitis* cultured from sputum
28								Spinal fluid: globulin (−), 6 cells
29	4.22	64	11,750	75	33	1/0	31	Spinal fluid Wa. R. and Kolmer pos.?
5/ 3								Blood Wa. R. 2 plus; Kahn pos.?
8	4.55	75	18,500	68	28	4/0		Urine: albumin (−); 3 pus/HPF
9	4.56	69	11,400	70	26	2/0	30	
10	4.70	69	12,400	69	26	3/0		
11	4.78	64	14,100	69	18	3/7		
12	4.77	64	12,200	69	19	4/4		
13	4.47	64	18,850	77	11	1/9		Urine: albumin (−); 4–5 pus/HPF
26	4.35	69	13,600	76	23	1/0	10	
6/ 7	5.72	69	16,250	52	39	5/4	28	Spinal fluid: Kolmer positive
24	5.08	69	14,450	83	17		1	
30								Urine: albumin pos.; 10 pus/HPF
7/ 8	4.95	69	16,200	76	22	1/0	2	
17	5.12	69	21,600	86	10		32	Urine: albumin (−); 1–4 pus/HPF
21	4.23	61	25,400	90	8		32	
28	3.35	52	20,750	88	11			
8/ 5	3.96	58						
7	5.40	68	20,100					
11	3.94	64	14,750	77	19		32	
14	4.82	69	13,400	76	22		24	
18	4.74	69	18,400	78	18	1/2	25	
22	3.79	64	20,800	76	20	2/1	28	
31	4.10	69	18,800	85	13	1/0	23	
9/ 6	4.36	64	19,100	90	9	1/0	27	
15	4.32	64	18,350	81	19		27	
22	4.36	69	30,300	89	11		28	Blood Wa. R. (−)
10/ 8	2.89	64	16,300	75	21	1/0	27	Spinal fluid: Culture neg.

(0.1 c.c. 1:1000 dilution) were strongly positive after 24 hours. Roentgenograms of the right foot revealed no pathological changes, but a chest plate showed an abscess cavity in the posterior portion of the left lower lobe. Pus was aspirated from several of the abscesses and cultured on Sabouraud's medium: the growth of *Coccidioides immitis* was confirmed by animal inoculation. One lesion was excised for pathological study. Cut section showed a central area of necrosis which was granular and slightly caseous, bounded by a narrow grayish zone. The histological report (Dr. David A. Wood) stated: "Section shows fatty and striated muscle tissue in which are large granulomatous areas and numerous abscesses. The granulomatous areas are characterized by broad zones of epithelioid cells and by centrally placed collections

of lymphocytes and necrotic debris. Spherules of *Coccidioides immitis* in various stages are present. Plasma cells and eosinophilic leukocytes are rather numerous."

The patient's course was generally downward although interrupted by a period of objective and subjective improvement during the time in which coccidioidin vaccine was administered. His temperature was persistently elevated, the daily maximum ranging from 99.6° F. to 101.6° F. (oral) except during the period of coccidioidin therapy when there were occasional elevations to as high as 104° F. During the first five weeks in the hospital there was rapid and progressive loss of weight and of strength. Treatment during this period consisted of supportive care, a vitamin barrage, supplemented by injections of liver extract, sedation and catharsis. On the thirty-ninth day of hospitalization he complained of "numbness and burning" of his feet and legs. At the same time he found it impossible to walk, owing partly to his general weakness, but also to the loss of proprioceptive sense in his lower limbs. The paresthesia and the loss of strength of the lower limbs extended upward progressively until, on the forty-eighth hospital day, urinary retention occurred. Control of the anal sphincter was lost one week later. Neurological examination at this time revealed the following significant findings: Bilateral absence of abdominal and Achilles tendon reflexes and marked weakness of the patellar reflexes; complete loss of superficial sensation over the feet and lower legs; inability to stand. The spinal fluid was clear and under no increase of pressure: microscopic examination and culture of the fluid were reported negative. On June 28, the seventy-fifth day of hospitalization, all reflexes below the costal margins were absent and sphincter control was completely lost.

A course of coccidioidin vaccine therapy was begun on May 23, the thirty-eighth day of hospitalization. Following preliminary skin and intramuscular tests for sensitivity injections of the vaccine were given intravenously on alternate days, beginning with a dose of 0.1 c.c. of a 1:1000 dilution and increasing the amount and strength given to a maximum dose of 2.0 c.c. of the undiluted vaccine. Twenty-three injections of undiluted vaccine in doses of 2.0 c.c. were given before the treatment was discontinued. Data concerning the dosage, the route of injection, and the reactions to individual injections are summarized in table 2. Whether because of the vaccine therapy, or because of a spontaneous remission in the course of the disease, during the first week in July there was a definite regression in the size of many of the subcutaneous abscesses. On July 14, for the first time in six weeks, the patient was able to void spontaneously and shortly thereafter his fecal incontinence became much less troublesome. Sphincter control was again lost after approximately four weeks and the patient was incontinent for the remainder of his illness.

During the entire period of hospitalization the patient suffered severe anorexia, persistent insomnia and frequent spells of "twitching and jumping" of the legs. There was a progressive weight loss and a mild degree of anemia for which three transfusions were given during the month of July. It became obvious that he was losing ground during the last week in August and his final days were characterized by a semimoribund state. He died on the one hundred and eighty-fifth day of hospitalization.

Autopsy (October 23, 1941). The body was that of a well-developed, but extremely emaciated negro male of about 40 years. There was a small subcutaneous thickening on the right side of the forehead. There was a small eschar from which pus could be expelled on the bridge of the nose. Over the thyroid cartilage was a sinus opening into the subcutaneous tissues. There were no enlarged palpable lymph glands. There were large and deep decubitus ulcers over the sacrum, over the right sacroiliac joint and over both greater trochanters. Similar ulcers were present over both external malleoli. There was a large subcutaneous abscess on the dorsum of the right foot. Thorax: Beneath the xiphoid process was a small abscess. There were extrapleural abscesses beneath the seventh and eighth ribs anteriorly on the

TABLE II

Coccidioides Vaccine Therapy

Dates	Vol. c.c.	Dilution	Route of Inj.	Reactions
5/23	0.1	1:1000	I.M.	No constitutional reaction. Slight local tenderness.
5/26	0.1	1:1000	I.V.	No local or systemic reaction.
5/28	0.2	1:1000	I.V.	Transient pains up arm and into chest after injection.
5/30	0.4	1:1000	I.V.	No reaction.
6/ 1	0.8	1:1000	I.V.	No reaction.
6/ 3	0.1	1:100	I.V.	No reaction.
6/ 5	0.2	1:100	I.V.	No reaction.
6/ 6	0.4	1:100	I.V.	No reaction.
6/ 7	0.8	1:100	I.V.	Noted unusual taste in mouth immediately after injection.
6/ 8	1.0	1:100	I.V.	Noted taste again. Stated that he can use legs better.
6/ 9	0.1	1:10	I.V.	Noted taste again. No constitutional reaction.
6/11	0.2	1:10	I.V.	No reaction.
6/13	0.4	1:10	I.V.	Taste in mouth. No other reaction.
6/15	0.8	1:10	I.V.	No reaction other than taste in mouth.
6/16	1.0	1:10	I.V.	Temperature to 102.6° F. following injection.
6/17	0.1	1:1	I.V.	No reaction.
6/19	0.2	1:1	I.V.	No reaction.
6/21	0.4	1:1	I.V.	No reaction.
6/23	0.8	1:1	I.V.	No reaction.
6/25	1.0	1:1	I.V.	Temperature to 102.6° F. Temperature to 104.2 on 6/26.
6/27	1.0	1:1	I.V.	Temperature to 103.4° F.
6/29	1.0	1:1	I.V.	Vomited 20 minutes after injection.
7/ 1	1.0	1:1	I.V.	No reaction.
7/ 3	1.0	1:1	I.V.	Temperature to 104.0° F. following injection.
7/ 5	1.0	1:1	I.V.	No reaction.
7/ 7	1.0	1:1	I.V.	No reaction.
7/ 9	1.0	1:1	I.V.	"Knees burn." No fever or systemic reaction.
7/11	1.0	1:1	I.V.	No reaction.
7/13	1.0	1:1	I.V.	No reaction.
7/15	1.0	1:1	I.V.	Nauseated and vomited afternoon following injection.
7/17	1.0	1:1	I.V.	Cold chill following injection: temperature to 104.2° F.
7/19	1.0	1:1	I.V.	Cold chill following injection: temperature to 101.6° F.
7/21	1.0	1:1	I.V.	No reaction.
7/23	2.0	1:1	I.V.	Temperature to 103.4° F. following injection.
7/25	2.0	1:1	I.V.	No reaction.
7/27	2.0	1:1	I.V.	No reaction.
7/29	2.0	1:1	I.V.	No reaction.
7/31	2.0	1:1	I.V.	Temperature to 103.0° F. in afternoon.
8/ 2	2.0	1:1	I.V.	Temperature to 100.4° F. following injection.
8/ 4	2.0	1:1	I.V.	No reaction.
8/ 6	2.0	1:1	I.V.	Temperature to 101.4° F. in afternoon.
8/ 8	2.0	1:1	I.V.	No reaction.
8/10	2.0	1:1	I.V.	No reaction.
8/12	2.0	1:1	I.V.	No reaction.
8/14	2.0	1:1	I.V.	No reaction.
8/16	2.0	1:1	I.V.	No reaction.
8/18	2.0	1:1	I.V.	Legs burn. Temperature to 100.4° F. after injection.
8/20	2.0	1:1	I.V.	No reaction.
8/22	2.0	1:1	I.V.	No reaction.
8/24	2.0	1:1	I.V.	Complains of "jumping in the legs."
8/26	2.0	1:1	I.V.	Complains of "jumping in the legs."
8/28	2.0	1:1	I.V.	No reaction.
8/30	2.0	1:1	I.V.	No reaction.
9/ 1	2.0	1:1	I.V.	No reaction.
9/ 3	2.0	1:1	I.V.	No reaction.
9/ 5	2.0	1:1	I.V.	No reaction.

right side and above the ninth rib on the left side of the thoracic cage. Both lungs were free except for a few strands of adhesions at the right base. The left pleural cavity contained half an ounce of amber fluid; the right pleural cavity, four ounces of similar fluid. On the right side of the chest posteriorly were four extrapleural abscesses, one at the inferior angle of the pleural cavity, the others adjacent to the eighth and ninth vertebral bodies. Exploration of these cavities with a probe revealed extensive destruction of the vertebral bodies and communication with the spinal canal. No opening could be found into the subarachnoid space and there was no evidence of communication with this space. There were no intrapleural abscesses. The lungs were grossly congested; no nodules or abscess cavities could be seen or felt. Pus was obtained from a moderately enlarged paratracheal lymph node. The heart was small and the valves were essentially normal. Abdomen: A half dozen pinhead sized abscesses were present on the anterior surface of the liver. The spleen, the stomach and the intestines were grossly normal. The kidneys were normal in size, but their surfaces were somewhat finely nodular. There were no nodules nor abscesses in the pelvis.

Organs (Dr. Alvin Cox): The left lung weighed 680 grams. Its pleural surfaces were smooth. Palpation of the lung revealed no nodules and the cut surface appeared normal except for moderate hyperemia and partial collapse posteriorly. One peribronchial lymph node contained a sharply defined cavity filled with white pasty material. A second, smaller lymph node was almost completely replaced by pale brown caseous material. The right lung weighed 780 grams and was similar to the left except for a subapical nodule 3 mm. in diameter with a central white opaque area and a peripheral gray remnant. In the periphery of the lower lobe was a less well-defined consolidated area 2 cm. broad. Nearby were indistinct gray nodules about 1 mm. in diameter. The bronchi and the pulmonary arteries showed no abnormalities. The spleen weighed 130 grams. The capsule was wrinkled and the pulp was normal except for a dozen sharply defined, calcified nodules up to 5 mm. in diameter. The liver weighed 2020 grams. The cut surface was normal. The portal vein branches were normal. The gall-bladder was normal. The kidneys together weighed 300 grams. The capsules stripped easily revealing mottled pale gray and dark red surfaces which were irregularly nodular. Clusters of pale yellow nodules protruded slightly and there were poorly defined pitted areas. The cut surfaces showed irregular gray streaks and spots, particularly in the cortices from whence some extended into the medullae. The pelves and ureters were thickened in spots.

Microscopic (Dr. Alvin Cox). Lungs: In the upper portion of the right lung just beneath the pleura was a large mass of acellular material about twice the area of a low power field surrounded by a dense fibrous capsule. This contained a moderate amount of black pigment in small clumps and scattered lymphocytes. Toward the inner surface were several multinucleated giant cells and fibrous tissue containing spherules of *Coccidioides immitis*. In other sections the lung lesions were more recent, composed of irregular areas of consolidation with an exudate of macrophages laden with brown pigment, lymphocytes and polymorphonuclear leukocytes. Elsewhere were areas of caseation with peripheral tubercle formation and early fibrosis. Here also were giant cells and spherules. No endosporulating forms were seen, but the organisms were otherwise characteristic of *Coccidioides* spherules. Peribronchial Lymph Nodes: Large caseous areas were bordered by a wall of dense fibrous tissue and giant cells, and spherules were present near the junction of tissue and caseous material. One spherule contained endospores. Satellite fibrous tubercles were present. Liver: Normal except for nodules described grossly. These had dense fibrous walls containing a few lymphocytes and centers composed of granular material which was extensively calcified. No spherules and no satellite lesions were found. Spleen: Two nodules one half centimeter in diameter had a structure similar

to the nodules in the liver. No spherules were seen. Kidneys: In large areas there were markedly irregular infiltrations of the cortical parenchyma by lymphocytes and polymorphonuclear leukocytes with scattered eosinophiles and macrophages. The tubules in the cortex were hardly visible in many places because of extensive collapse and atrophy: a few tubules were dilated and contained pus. The glomeruli were less altered and many appeared normal. There was a diffuse increase in interstitial tissue throughout. This was most marked in the medulla where cellular infiltration was slight. No *Coccidioides* spherules were seen. Other parts of the kidneys showed an essentially normal structure.

Pathological Discussion. The lesion in the upper part of the right lung had the appearance of a primary focus whereas the other granulomatous lesions in the lung were more recent and progressive. The lymph node lesions were like the old lung lesion, although, if they were part of a primary complex, it is difficult to explain their presence on the side opposite to that of the lung lesion and their absence on the same side. However, there may have been other involved mediastinal nodes and it is possible that retrograde spread along lymphatic pathways occurred from these. The nodules in the liver and in the spleen had a different appearance and were, presumably, not caused by the fungus. They did not resemble syphilitic lesions. The presence of one small lesion in a splenic vein branch suggested that some or all of these calcified nodules may have been phleboliths. The pyelonephritis was independent of the coccidioidal granuloma and was probably an important cause of death.

Discussion

A considerable number of the common features of disseminated coccidioidomycosis are demonstrated by this case. Dark skinned races exhibit a greater tendency to develop the disseminated form of the disease than does the white race. The disease is acquired by inhalation of the fungus (chlamydospores) and the transmission of coccidioidomycosis from man to man is unknown. The patient had always lived in the proximity of known endemic areas and he had frequently traveled through these areas. The attack of "flu" which preceded the appearance of the subcutaneous abscesses was undoubtedly a manifestation of coccidioidomycosis, but it is somewhat doubtful that it represents a primary infection as the patient had been an inmate of a city prison in a non-endemic area for some weeks previously. However, in the usual case, dissemination generally follows shortly after the infection has been acquired.

The terminal illness was characteristic of disseminated coccidioidomycosis. There was the typically slow progression downward punctuated by periods of relative remission. The course was febrile throughout. Severe anorexia was accompanied by progressive weight loss and terminal cachexia. Multiple decubitus ulcers developed during the last month. Despite the liberal use of vitamins, liver extract and various iron preparations there was a persistent anemia which responded only temporarily to blood transfusions. The organs whose involvement gave rise to clinical symptoms were those commonly involved during dissemination by the fungus, namely, the lungs, the integument and the skeletal system, including both the bones and the muscles.

The paraplegia was undoubtedly the result of pressure on the spinal cord by the abscesses which eroded through the vertebral bodies from the extrapleural space into the extradural space. There was no evidence that the patient's syphilis played any rôle in the neurological symptoms. It is unfortunate that permission to open the cranial vault and the spinal canal was not obtained, but

TABLE III

Complement Fixation and Precipitin Tests for *Coccidioides immitis* on Serum in the Case Here Reported

Dates	Complement Fixation Tests (serial dilutions of .25 c.c. of serum)							Precipitin Tests (serial dilutions of antigen)				Remarks
	1:2	1:4	1:8	1:16	1:32	1:64	1:128	Undil.	1:10	1:40	1:100	
5/15/41	++++	++++	++++	++++	++	0	0	+++	++	0	0	Strong complement fixation with definite but lower precipitin titer, characteristic of disseminated coccidioidomycosis.
5/20/41	++++	++++	++++	++++	++	0	0					
6/10/41	++++	++++	++++	++++	+++	+	0					
7/10/41	++++	++++	++++	++++	+++	++	0					
7/29/41	++++	++++	++++	+++	++	+	0	++++	+++	+++	+	No significant change in titer of complement fixation but a definite rise in precipitins.
8/16/41	++++	++++	++++	++	+	+	0	++++	+++	+++	+	No significant change.
9/ 2/41	++++	++++	++++	++++	++	+	0	++++	+++	+++	+	No significant change.

sterile cultures of spinal fluid removed four days before death minimize the possibility of intrathecal involvement. In about 25 per cent of the cases of disseminated coccidioidal infection there is involvement of the central nervous system.[2]

Various observers have treated coccidioidal infections with vaccines consisting of ball-mill grinds of the fungus. Results have been equivocal with Jacobson [3] reporting the most consistently favorable results. Such a vaccine was tried on this patient with the utmost skepticism and the dosage and the intervals of treatment were limited to those previously reported in the literature. It is recognized that the subjective and objective improvement which accompanied the use of the vaccine may have represented an ordinary remission in the course of the disease. However, the degree to which the subcutaneous lesions diminished and the relief of neurological symptoms, indicating a similar recession of the abscess pressing upon the spinal cord, demonstrated a degree of regression which is not noted frequently in this disease. Even more impressive than these objective changes were the subjective improvement during this period of treatment with vaccine, the improvement in appetite, the regaining of strength and the boost in the patient's morale. It would seem that, in the absence of any effective chemotherapeutic agent, a trial of vaccine would be indicated in any case of disseminated coccidioidomycosis. Furthermore, there is no evident contraindication to the use of greater doses of vaccine than have hitherto been reported.

The clinical course of disseminated coccidioidomycosis is ordinarily indistinguishable from that of disseminated tuberculosis, or of other mycoses. The diagnosis is established by the recovery of *Coccidioides immitis* from specimens of sputum or pus, or the demonstration of the typical *Coccidioides* spherules in tissue sections. Identification of the fungus depends upon the demonstration of its diphasic character by culture and animal inoculation with the recovery of spherules from a guinea pig or mouse. Sabouraud's medium or the special medium developed at Stanford University [1] are particularly useful for the cultivation of *Coccidioides immitis*. Either guinea pigs or mice can be used for animal inoculation; intraperitoneal or subcutaneous injection of material is satisfactory. The coccidioidin skin test, analogous to the tuberculin intradermal test, is useful for screening patients, although its specificity has been questioned recently. Emmons [4] has shown that a cross-sensitivity exists with the fungus, *Haplosporangium parvum*. Complement fixation and precipitin tests are valuable for following the course of the disease. Both tests are almost always positive in severe infections. Although the precipitins are poorly demonstrable in most disseminated infections, the titer of the complement fixation ordinarily rises parallel to the severity of the infection. In the case presented all laboratory aids were utilized and all were positive for the disease. The results of repeated precipitin and complement fixation tests performed on the patient are summarized in table 3.

Summary

1. A case of disseminated coccidioidomycosis with fatal termination is presented.

2. Points of particular interest are (a) the paraplegia resulting from pressure of an extradural abscess on the spinal cord, (b) the rather complete clinical and laboratory observations, and (c) the trial of coccidioidin vaccine therapy.

3. In the absence of any useful chemotherapeutic agent, the further trial of coccidioidin therapy in the disseminated disease is suggested.

The author expresses his appreciation to Dr. Leo L. Stanley, Chief Surgeon (on leave of absence), California State Prison, San Quentin, and to Drs. Charles E. Smith, Alvin Cox and David A. Wood of the Stanford University School of Medicine for their assistance in the study of this patient.

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FAMILIAL MYASTHENIA GRAVIS *

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THE etiology of myasthenia gravis is still a much debated question. The influence of heredity on the disease has not been accepted by the great majority of observers. Authorities like Ford,[1] Cruschman,[2] McCarthy,[3] Wilson,[4] Wechsler,[5] Campbell and Bramwell[6] have rejected it and Viets[7] hesitated to pass an opinion. However, Keschner and Strauss[8] suggest a congenital disposition to the disease; and Bing,[9] Riley and Frocht,[10] Marinesco,[11] Hart,[12] and Rothbart,[13] each reporting cases of familial myasthenia gravis, believe in some hereditary influence.

Since the only way to prove or disprove each theory is to add more case reports to the few on record, without entering into the question, I should like to add to the others one more instance of familial myasthenia gravis.

CASE REPORTS

Case 1. A. T. was a 38 year old woman, born in the United States of Albanian parentage, married, with three children. Her father died of cerebral hemorrhage at 67; her mother died of complications from an abdominal operation at 40; two brothers and one sister were living and well; another sister was affected by the same disease. The patient had had measles and whooping cough as a child but had been otherwise healthy. She married at 20 and went through two normal pregnancies.

Ten years before admission she went to work in a radio factory and was employed in a room in which the temperature was kept at an exceedingly high level. She attributed the onset of her disease to this cause. After being employed there for six or seven months she gradually became weaker and weaker, being completely exhausted at night. She gave up her job but her symptoms did not improve. The eyelids began to droop; she noticed a slight strabismus and was so weak, especially during her menstrual periods, that she became almost helpless.

* Received for publication May 17, 1944.

With the event of her third pregnancy she made a marked improvement, and gave birth at term to a healthy child. A few weeks after delivery, however, all of her symptoms returned more aggravated than before. She could barely talk or swallow; the slightest effort exhausted her; the limbs became cold and heavy, and she was practically helpless.

On physical examination the patient was quite obese. Color and expression were fair. There was a marked drooping of the eyelids and a pronounced strabismus. The thyroid was slightly enlarged. Pulse was 85 and of good quality. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic. The heart and lungs were normal. The abdomen was soft. The muscles were flabby and the ordinary reflexes normal. Blood count was normal; blood chemistry normal; Wassermann reaction negative; urinalysis normal. The basal metabolic rate was — 10. Radiography was negative for mediastinal tumor or other signs of enlarged thymus.

The patient was put on prostigmine bromide tablets with a slight improvement. The medication was changed to prostigmine methylsulphate hypodermically with a spectacular amelioration of all symptoms. Using two ampules a day for two weeks, she became stronger each day. The dose was gradually reduced until she was again put on prostigmine bromide tablets. At the time of this report she was almost well and was using the medicine only during menstrual periods or when an occasional symptom reappeared.

Case 2. Rose S., sister of the preceding, was 28, single. She had had measles and pneumonia as a child, and a tonsillectomy when nine years old. She had been healthy and normal up to the age of 18, when she went to work with her sister in the same factory and under the same conditions. She also attributed her disease to the work.

The symptoms in her case were more rapid and more severe. She became bedridden with marked ptosis, severe dysphagia, difficulty in speaking and using her limbs. During an attack of head cold she almost choked trying to cough up some mucus. Often she could hardly breathe.

Physical examination showed no abnormalities except the ptosis and the extreme flabbiness of the muscles of the limbs. The only abnormal laboratory finding was an occasional slight excess of creatinine. Roentgen-rays of the chest were negative.

This sister was put on prostigmine methylsulphate, hypodermically administered, with moderate results immediately. The addition of ephedrine and potassium salts did not help much. There were slight remissions when she was able to get along with the tablets of prostigmine bromide, but usually she had to revert to the ampules, requiring occasionally some atropine to relieve the increased peristalsis.

Summary

Myasthenia gravis in two sisters is reported. Prostigmine was very effective in one but not in the other. Inasmuch as we know that remissions are common in the disease, the improvement of the first sister may be due to prostigmine or to the natural course of the disease. Both sisters noticed their symptoms for the first time after working in a greatly overheated room. Even if this is a coincidence, it is a very unusual one and should be reported.

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ACUTE LUPUS ERYTHEMATOSUS DISSEMINATUS: A REPORT OF A CASE IN A MALE WITH ASSOCIATED ATYPICAL VERRUCOUS ENDOCARDITIS (LIBMAN–SACKS) *

By S. Gilbert Blount, Jr., M.D., and John T. Barrett, 1st Lt., M.C., A.U.S.

The present concept of the symptom-complex known as acute lupus erythematosus disseminatus has been formulated over the period of the last 100 years.

Hebra,[1] in 1845, first described lupus erythematosus as a local cutaneous lesion under the name "seborrhea congestiva." Six years later Cazenave [2] gave the disease its present name. It was not until 1872 that Kaposi [3] subdivided the disease into "lupus erythematosus discoides" and "lupus erythematosus discretus and aggregatus." He was the first to realize the generalized and systemic manifestations of the latter form with its attending grave prognosis, as three of his 11 cases died while under observation. The clinical picture as we know it today was, in general, adequately described by this early investigator.

Sir William Osler,[4] in 1895, published the first of three series of cases under the heading "On the Visceral Manifestations of the Erythema Group of Skin Diseases," the other series being reported in 1900 [5] and in 1904.[6] It was Osler who initiated the modern investigation of this syndrome; in particular, as regards the visceral and general systemic nature of the condition.

In 1924 Libman and Sacks [7] first recognized and described a "hitherto undescribed form of valvular and mural endocarditis" or "atypical verrucous endocarditis."

Since 1924 this clinico-pathologic entity has been widely and thoroughly studied both from the clinical and the pathological standpoints with considerable lack of unanimity of opinion as to its clinical manifestations or the pathological

* Received for publication April 29, 1944.

findings. Klemperer, Pollack, and Baehr,[8] however, in 1941, presented a thorough study of both the gross and histological pathology of the disease that provides a firm pathologic foundation.

Case Report

G. T., an American schoolboy of Italian parentage, was first admitted to the Rhode Island Hospital on July 14, 1943, at the age of 15, complaining of fever of two weeks' duration.

Present Illness. Seven months before admission the patient experienced painful swelling of the right ankle which prevented walking. This cleared up within a few days and the patient was symptom free until four weeks before entry. At that time his right knee became swollen and painful; however, this disappeared within a week under home treatment.

Beginning 14 days before admission there was a gradual onset of fever which was continuous in nature and reached its height during the late afternoon. During this period his appetite waned and he felt nauseated on several occasions, but there was no actual vomiting. Bowel habits were unusual in that the patient had from one to three stools a day, not accompanied by abdominal cramps. The stools at no time contained blood or mucus. For the week preceding entry the patient complained of pain in his ribs, particularly at the right costal margin. This pain was accentuated by deep breathing. For two or three days prior to admission the patient developed a hacking, non-productive cough. A history of a 20-pound weight loss in the two months preceding admission was obtained. He consulted two different doctors, and was given some large white pills which he was told were "good for infection." The patient took two of these pills every four hours for the four days before entry. There was no apparent effect on the elevated temperature and the patient was referred to the hospital.

Past History. The patient stated that he had been healthy most of his life. There were no acute infections or diseases since early childhood. He had had the usual childhood exanthemata, but gave no history of rheumatic fever, chorea, scarlet fever or diphtheria. He underwent a tonsillectomy at the age of seven because he was sickly and was having frequent colds. This was followed by subjective improvement. Seven months before admission the patient had an "infection" of the middle and index fingers of the right hand which required a month to heal without specific treatment.

Family History. The father had tuberculosis and had undergone a three-stage thoracoplasty in a local sanatorium. He was discharged from the sanatorium one and one-half months before the patient's entry. There was no history of other disease or allergic manifestations.

Review of the Systems. A careful review of the systems elicited nothing of significance.

Physical Examination. Pulse 120. Respirations 30. Temperature 104.8° F. Blood pressure 110 mm. Hg systolic and 30 mm. diastolic.

The patient appeared to be large for his age and showed signs of obvious weight loss. He lay flat in bed in no distress. No jaundice or cyanosis was present. The face appeared flushed and the skin over the V of the neck and over the wrists revealed small, pigmented, plaque-like areas.

Head. There were no scars, deformities, or mastoid tenderness.

Eyes. Pupils were round, regular, and equal, reacting to light and accommodation. There was no nystagmus. There was slight scleral injection. Examination of the fundi revealed nothing remarkable.

Ears. There was no discharge or redness. The tympanic membranes were not unusual.

Nose. There was no discharge or obstruction. The septum was intact.

Mouth. The teeth were in fair repair. The tongue was heavily coated. The papillae were enlarged.

Pharynx. Considerably reddened, particularly in the area of the tonsils and the anterior pillars.

Neck. There was no stiffness. There was moderate enlargement of the lymph nodes in both anterior and posterior cervical chains. The trachea was in the midline without tug. The thyroid was not palpable.

Spine. There were no structural deformities. There was slight costo-vertebral angle tenderness on the left.

Thorax. There were no structural deformities. Expansion was full and equal with respiration.

Lungs. Clear to auscultation and percussion. There were no râles.

Heart. Heart was not enlarged to percussion and apical impulse was felt at the nipple line. No thrill or shock was detected. Sounds were of good quality. There was a systolic murmur heard at the apex and in the aortic region, which was not transmitted. No diastolic murmur was detected. P_2 was greater than A_2. M_2 was greater than M_1. Rate was rapid and rhythm regular.

Abdomen. Soft, no spasm or tenderness. Liver, spleen, and kidneys were not palpable. No masses were felt.

Genitalia. Normal adult male.

Rectal. Rectal sphincter tone was good. Prostate was not enlarged. There was no blood on the examining finger.

Reflexes. Rather sluggish, but equal throughout.

Extremities. There were no swollen, tender or warm joints. There was no edema. Fingers were slightly suggestive of a fusiform shape. No subcutaneous nodules were felt.

Course. During the first week the patient remained a diagnostic problem. The temperature was suggestive of a septic infection, spiking daily to about 103° F. and never below 100.5° F. The pulse increased proportionately, running between 100 and 110. The laboratory examinations revealed some interesting findings: a persistently low white cell count, a marked anemia, and a negative blood culture.

On the seventh hospital day a peculiar rash developed over the bridge of the nose and cheeks, butterfly-like in design. It was at this time that the diagnosis of acute lupus erythematosus disseminatus was first suggested.

Examination of the fundi now revealed blurring of the disc margins with elevation of about 1½ diopters. This was present in both fundi and was interpreted as bilateral papilledema.

During the next week there developed a stomatitis and beginning ulceration of the posterior wall of the pharynx. He perspired profusely during the morning hours and complained rather bitterly about a sore throat. Although his general condition was becoming weaker, he voiced no other complaints. On the fourteenth hospital day he was tested with Old Tuberculin 1:10,000, which was read as negative. On the eighteenth day the patient had an acute episode consisting of chills and fever to 105.4° F. The skin lesions on the face, hands, and neck became more pronounced. Respirations and pulse rate were increased and the patient appeared extremely sick.

Examination of the lungs revealed them to be clear to auscultation and percussion. The cardiac murmur detected on admission was still present and there was noted for the first time a gallop rhythm which persisted until death. That night the patient had a nose bleed which was stopped with some difficulty. During this time the anemia became more marked, and a platelet count was reported as 100,000 per cu. mm. Two electrocardiograms were reported as showing changes indicative of an acute process and not inconsistent with the diagnosis of pericarditis.

The only treatment during this time was of a supportive nature, consisting of a diet high in carbohydrate and vitamin content with added parenteral vitamins. Several blood transfusions were given and pentnucleotide was started with the idea of combating the leukopenia. During this period the urine was not remarkable, showing only a trace of albumin, a specific gravity ranging from 1.010 to 1.020 with only a rare red blood cell and 2 to 100 white blood cells per H.P.F. in centrifuged specimens.

On the twelfth hospital day sulfadiazine, 1 gram every four hours, was started on an empirical basis. However, it was soon found to be ineffective and was stopped on the eighteenth day. At that time the patient became mentally cloudy and disoriented and this condition persisted, more or less, until death. Up until that time the patient had been taking fluids well, but then, with few exceptions, fluids and diet had to be forced.

On the twenty-second day he complained of difficulty in breathing and shortly afterwards coughed up a large clot of blood, after which he felt better. Respirations dropped from 36 to 24. On the same day the nurse reported rectal bleeding. It seemed as though a generalized bleeding tendency was present. During that week the temperature ranged daily from normal to 103.5° F., the spike usually occurring about 7 a.m.

The last week of the patient's life was one of a rapid and progressively downward course. The anemia became very marked despite transfusions. The red blood cell count fell to 870,000 per cu. mm. and the hemoglobin to 2.5 grams per 100 c.c. of blood (Sheard-Sanford). The white blood cell count dropped to 2,000 per cu. mm. with 65 per cent polymorphonuclear leukocytes, and 33 per cent lymphocytes. He became very restless and uncoöperative. There was a marked ulceration about the anterior pillars and in the tonsillar regions, with ulceration and soreness of the mouth. Bleeding of the nose and mouth was observed on several occasions. On the twenty-sixth day the patient was very drowsy, complained of difficulty in breathing and pain in the abdomen.

On the day before death the patient stated that he felt fine and he looked better than he had during the preceding 10 days. Examination of his heart on this day revealed a gallop rhythm and sounds definitely suggestive of severe myocardial damage. There was slight dullness to percussion at both lung bases with breath sounds diminished over these areas. No definite râles were heard. The temperature continued to spike during the last week with the patient perspiring profusely.

On the day of death the temperature rose to 106° F. for a 24 hour period. On the evening of the thirty-second hospital day, 10 minutes after the cessation of a blood transfusion, respirations became labored, the pulse weakened, and the blood pressure fell to 80 mm. Hg systolic and 50 mm. diastolic. The patient was confused, cold and sweating. He was given oxygen and Eschatin intravenously. The general condition became somewhat better; however, he rapidly grew worse and died at 7:00 p.m.

During the entire hospital stay the urine output remained adequate, the patient voiding over 1500 c.c. of urine a day. Five blood cultures were reported as negative with one blood culture, taken on the day of death, reported as containing very many colonies of *Staphylococcus aureus,* coagulase positive. On that day the blood examinations showed the hemoglobin to be 2.3 grams per 100 c.c. of blood with 1,000 white blood cells, of which only 1 per cent was polymorphonuclear leukocytes and 99 per cent were lymphocytes.

Urinalysis. On 15 occasions the urine was analyzed. Reaction was at all times acid. Specific gravity varied between 1.005 and 1.020. The sediment revealed rare hyaline casts during the first 10 days. During the last two weeks of life the sediment revealed many hyaline and a few granular casts. Red blood cells were rarely observed (4–6 H.P.F.), whereas white blood cells varying from occasional to 15–100 were reported on all occasions. Sulfadiazine crystals were at no time seen.

TABLE I

Blood	R.B.C.	Hgb.	W.B.C.	Polys	Lymphs	Platelets
7–13–43		6.3	3260	73	26	
7–14–43	2.94	9.2	3950			
7–15–43			4075			
7–22–43	2.64	10.1	4200			100,000
7–23–43	2.7	10.1	1900	77	14	
7–27–43	3.23	8.7	2150	66	32	
7–29–43	2.22	8.6	2100			
8– 4–13			2800	67	31	
8– 5–43			3300	66	33	
8– 8–43	870,000	2.5	2070			
8–12–43		5.2	1550			
8–14–43		3.8	1000	1	99	

TABLE II

Blood	B.U.N.	Glucose	Total Protein	Blood Cultures	Sedimentation Rate		Serology
					½ hr.	1 hr.	
7–14–43	13	70			50 mm.	55 mm.	
7–15–43				Sterile			Hinton negative
7–17–43				Sterile			
7–19–43				Sterile			
7–21–43					40 mm.	58 mm.	
7–23–43			6.2				
7–24–43			6.2				
7–28–43					26 mm.	35 mm.	
7–31–43				Sterile	58 mm.	63 mm.	
8– 5–43					81 mm.	85 mm.	
8–11–43					60 mm.	78 mm.	
8–14–43				Staph. aureus. Very many colonies. Coag. pos.			

Cultures. Nose and throat negative for hemolytic streptococcus (7–17–43). Feces negative for typhoid and dysentery group (7–20–43). Throat—*Streptococcus viridans* predominate (7–20–43). *Staphylococcus aureus* coagulase negative. Smear from lesion in mouth (7–23–43). Few fusiform rods. No spirillum seen.

Other laboratory adjuncts: Feces Guaiac negative (7–23–43). Old tuberculin test 1:10,000 negative on 7–27–43.

Roentgen-ray. (7–14–43). Examination of the chest showed slight accentuation of the structures in the region of the lung roots and accentuation of the markings particularly at the bases, but the lungs showed no active pathologic lesions. There was no fluid in the pleural cavities. The left cardiac contour was straighter than normal, and there was a slight bulge in the region of the left auricle which was consistent with rheumatic heart disease.

Electrocardiograms. (7–14–43). The tracing showed a rapid, regular action. The P–R interval time was at the very upper limits of normal. $ST_{1, 2 \text{ and } 3}$ showed slight elevation with upright T waves. The record was somewhat abnormal and there were changes suggestive of an acute process. Rate 110. (7–26–43). Since the tracing of 7–14–43 there had been some changes. ST_1 previously upright only slightly elevated now approached the base-line, and T_1 previously upright was

inverted. The second and third leads showed no significant changes, but in the fourth lead T_4 previously upright was now inverted. These changes were indicative of an acute process, and were not inconsistent with pericarditis. Rate 104. (7–30–43). The action was rapid but regular. Rate 117. There were two previous records, July 14 and 26. The changes were of minor significance. The record still suggested a possible pericarditis.

FIG. 1. *Heart.* Note the infiltration with lymphocytes containing pyknotic nuclei.

Autopsy Findings: Gross Findings. The postmortem examination was performed two hours after death. The body was that of a well developed, fairly well nourished white adolescent male measuring 175 cm. in length. The skin showed many fine transparent blebs over the body which measured up to 3 mm. in greatest diameter. There was an excoriated and crusted area at the base of the right nostril. A decubitus ulcer, measuring 4 cm., was present on the right buttock.

Serous Cavities. The peritoneal cavity contained 200 c.c. of a light yellow fluid. The peritoneum was thick, white, and opaque. The splenic flexure of the colon was adherent to the lateral wall. Each pleural cavity contained 150 c.c. of a light yellow fluid. The parietal pleura was thick, white, and opaque, and showed many petechial

hemorrhages throughout. The pericardial cavity contained 100 c.c. of a light yellow fluid. The pericardium, too, was thick, white, and opaque, and showed a few hemorrhagic areas measuring 3 mm. in greatest diameter.

Heart. The heart weighed 360 grams. The epicardium showed a number of petechial hemorrhages measuring up to 1 mm. and two localized areas of thickened visceral pericardium measuring up to 2 cm. The endocardium of the auricles and left ventricle was generally thickened and opaque. The heart was entirely normal

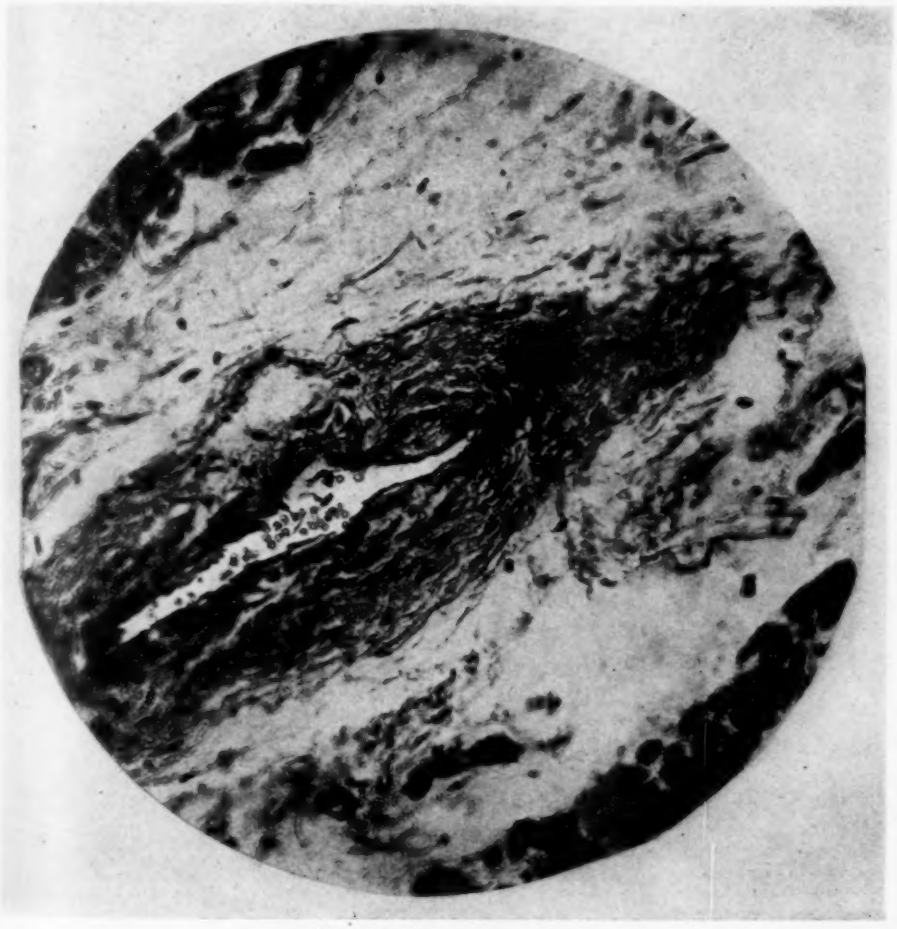

FIG. 2. *Blood vessel in the myocardium.* The "fibrinoid degeneration" present in the adventitia of the vessel wall is especially prominent at the right of the lumen.

macroscopically except for the above findings and the mitral valve which, at its line of closure, showed two small, firm projections measuring 1 to 2 mm. across. At the base of the mitral valve, just above its insertion, there were three similar larger areas measuring 3 mm. across. The mitral valve generally was granular in appearance.

Lungs. The lungs weighed 470 and 480 grams. On section, the parenchyma was a peculiar brownish color with numerous hemorrhagic areas measuring up to 1 cm. in diameter.

Spleen. The spleen weighed 360 grams. It was firm in consistency and its periphery showed irregular white, somewhat fibrous areas measuring up to 2 cm. in diameter.

Gastrointestinal Tract. The first part of the duodenum showed a number of hemorrhagic areas in the mucosa. The large intestine was filled with "tarry" fecal matter.

Pancreas. The pancreas was firm in consistency and dark brown in color.

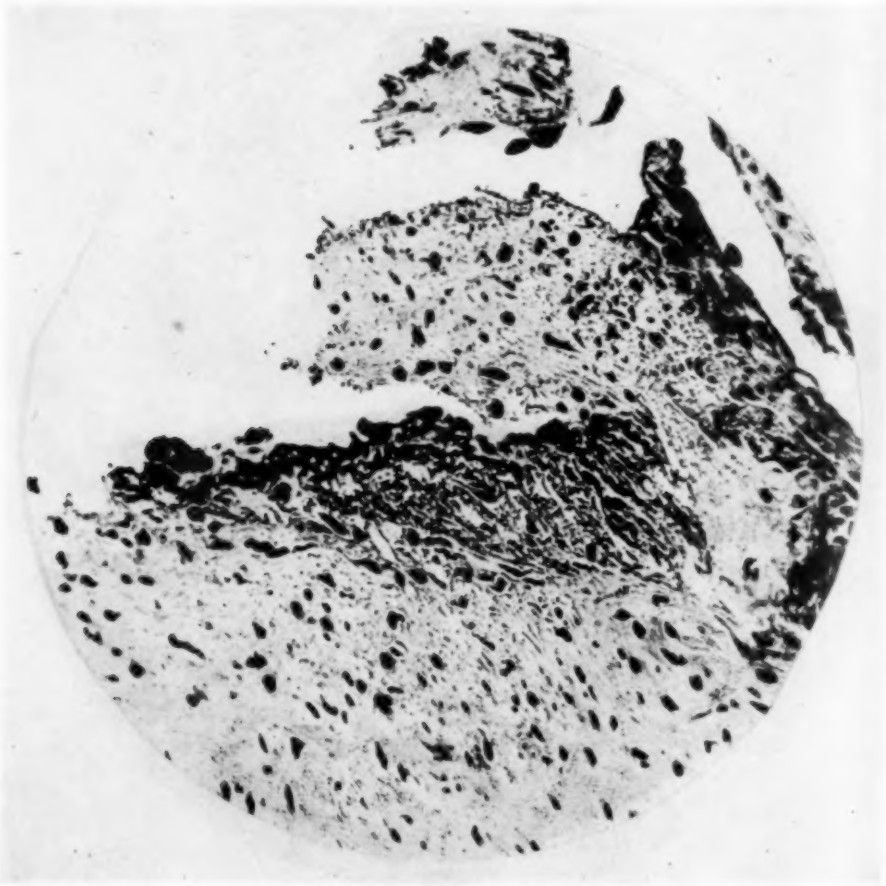

FIG. 3. *Heart valve.* Necrosis and hemorrhage may be seen in the subendothelial area. A thrombus is present which, at the left, is torn away.

Liver. The liver weighed 1920 grams. The right border was inordinately pale and showed many small hemorrhages beneath its capsule measuring up to 1.5 cm. The lateral portion of the right lobe showed a typical "nutmeg" appearance.

Kidneys. The right kidney weighed 270 grams; the left, 280 grams. The capsule was slightly adherent. The cortex was pale, measured up to 1 cm., and showed many small hemorrhagic areas.

Bladder. The bladder was not remarkable.

Aorta. The aorta was smooth and glistening and elastic.

Brain. The brain weighed 1270 grams. Except for a small amount of subarachnoidal congestion, it was grossly not unusual. The pituitary was not remarkable.

Bone Marrow. The bone marrow from the vertebrae was soft, almost liquid in consistency, and red in color. That from the upper one-third of the humerus was brown with some fat. The marrow from the ribs was red and scanty.

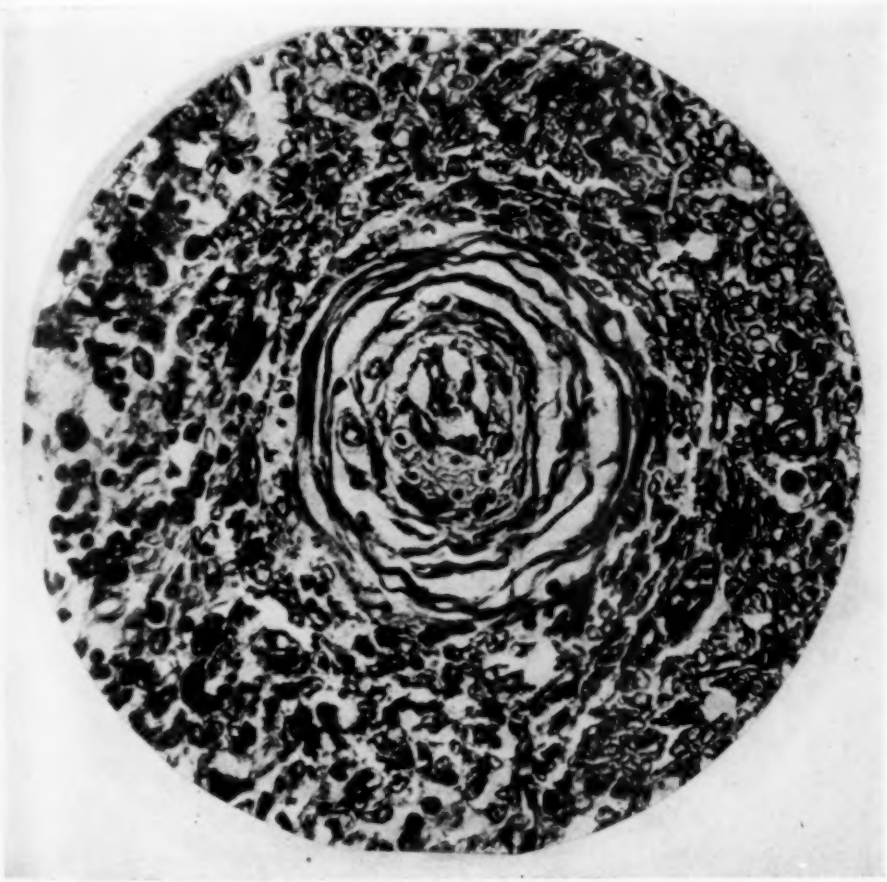

FIG. 4. *Spleen.* The periarterial fibrosis in "onion-skin" arrangement is especially prominent. Endothelial proliferation is present, almost completely occluding the lumen.

Lymph Nodes. The mesenteric lymph nodes measured up to 1.5 cm. and showed necrosis. A large group of nodes was present about the tail of the pancreas. These, too, showed necrosis.

Thyroid. The thyroid gland was not unusual.

Microscopic Findings: Heart. The pericardium showed thickened collagenous material beneath its mesothelial surface. This showed granular, deeply eosinophilic masses of "fibrinoid degeneration" as described by Klemperer, Pollack, and Baehr.[8]

The epicardium showed "fibrinoid degeneration." In the myocardium was a sparse infiltration with lymphocytes and plasma cells with pyknotic nuclei (figure 1). The small and large vessels in the myocardium presented the appearance of "fibrinoid degeneration" (figure 2). Sections of the lesions seen grossly in the mitral valve

showed the typical "fibrinoid degenerative" changes with one section revealing an organizing thrombotic process (figure 3). In one area was a slight amount of necrosis and hemorrhage beneath the endothelial surface. There was no cellular reaction present. No evidence of rheumatic fever was seen.

Lungs. In the blood vessels and peribronchiolar areas there was "fibrinoid degeneration." The alveolar walls were slightly thickened with an occasional leukocyte.

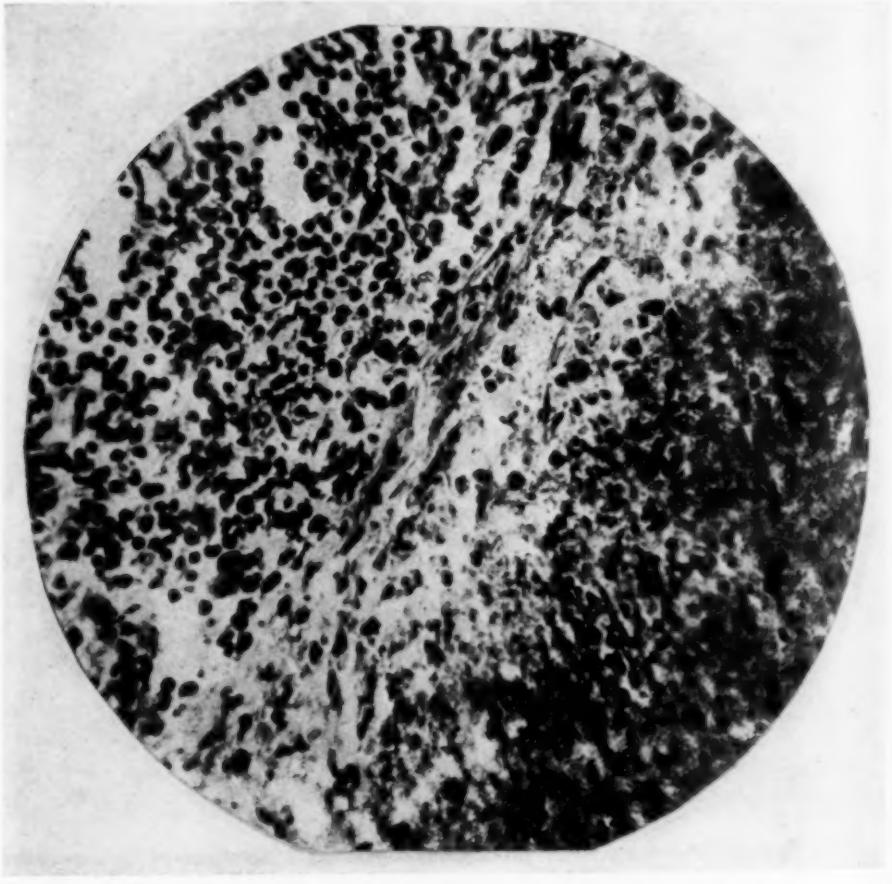

FIG. 5. *Lymph node.* The necrosis is seen in the right-hand half of the photomicrograph.

Spleen. The striking feature seen in the spleen was a peculiar periarterial fibrosis involving the central and penicilliary arteries. This was arranged in concentric rings giving an onion-skin appearance (figure 4). A small amount of endothelial proliferation was seen in a number of the penicilliary arteries. There was a generalized extravasation of red blood cells into the reticulum. Large areas of necrosis were seen.

Gastrointestinal Tract. "Fibrinoid degeneration" was seen in the submucosa. Some slight hemorrhage was present in the mucosa of the small intestine.

Pancreas. Some "fibrinoid" changes were seen in the perivascular areas and involving the trabeculae.

Liver. A marked amount of passive congestion destroyed the hepatic cells in the central area. Large masses of bacteria were present surrounded by necrosis but showing no leukocytic reaction. This peculiar finding may be explained by the bone marrow histology (see below). Again some slight "fibrinoid" changes were present in the portal areas.

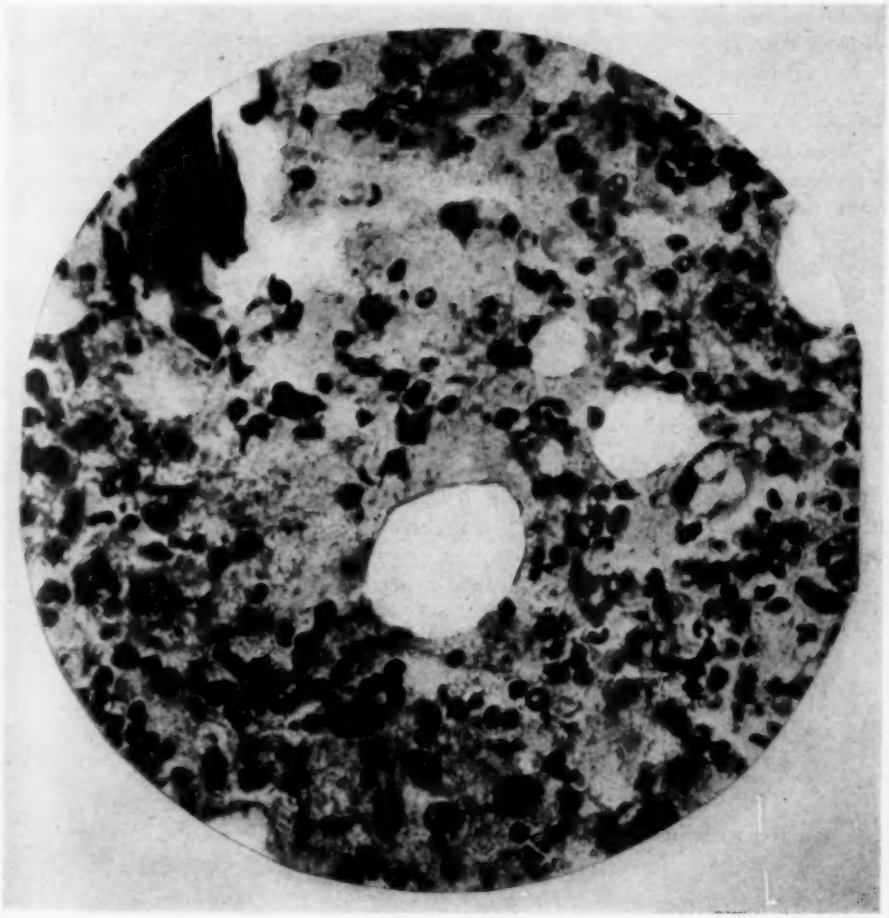

FIG. 6. *Bone marrow.* The cells are sparse with pyknotic nuclei and other degenerative changes. The granulopoietic series is almost entirely absent. The peculiar granular and gelatinous degeneration is present throughout the entire field.

Kidneys. The glomeruli were cellular and avascular. Such capillaries as remained were congested. An occasional polymorphonuclear leukocyte was seen in the tuft. Some glomerular tufts showed a slightly thickened pericapillary connective tissue. These changes, we believe, are significant, even though they do not approach the "wire loop" appearance described by others. "Fibrinoid degenerative" changes were present around the vessels, but not as marked as in other organs. The acute glomerulitis was interpreted as being a part of the terminal staphylococcic septicemia.

Adrenals. Some thickening of the capsule with "fibrinoid" changes was seen.

Bladder. The "fibrinoid degeneration" seen elsewhere involved the bladder wall. This was especially marked in the submucosa and adventitial coats.

Genitalia. The interstitial tissues of the testicle showed "fibrinoid" changes.

Thyroid and Thymus. Both organs showed the changes in their connective tissues described in other organs.

Brain. The meninges were thickened with "fibrinoid degenerative" alteration. The blood vessels had a marked eosinophilic staining reaction in their walls slightly resembling changes seen in periarteritis nodosa. No perivascular leukocytic reaction was present.

Skin from Abdomen. "Fibrinoid" changes were again seen in the corium.

Lymph Nodes. Necrosis was present in the majority of sections (figure 5). No evidence of tubercle formation was found.

Bone Marrow. The predominant feature was a peculiar granular and gelatinous-like degeneration. A marked decrease in the granulopoietic series was seen and although small foci of erythropoietic tissue were present, the nuclei were pyknotic and showed karyorrhexis (figure 6).

Diagnosis: Acute disseminated lupus erythematosus. Acute glomerulonephritis (early). Multiple petechial hemorrhages of the lungs. Interstitial bronchopneumonia. Necrosis of the spleen and lymph nodes. Interstitial non-suppurative myocarditis. Atypical verrucous endocarditis (Libman-Sacks). Focal necrosis of the liver. Chronic passive congestion of the liver. Hydroperitoneum, hydropericardium and hydrothorax (slight). Thickening of the pleura, pericardium and peritoneum. Multiple petechial hemorrhages of the pericardium, epicardium, pleura and liver.

Comment on the Clinical and Pathological Aspect of the Case. Although the occurrence of this entity is unusual in a male subject, analysis of the clinical data and course would seem to justify the diagnosis of acute lupus erythematosus on a clinical basis alone.

Review reveals the following clinical aspects:

1. Onset with polyarthralgia.
2. Septic febrile course.
3. Polyserositis.
   - *a.* Pleurisy.
   - *b.* Pericarditis.
   - *c.* Abdominal pain.
4. Gastrointestinal disturbance.
   - *a.* Anorexia.
   - *b.* Nausea.
   - *c.* Diarrhea.
5. Bleeding tendency.
   - *a.* Oral and nasal bleeding.
   - *b.* Hemoptysis.
   - *c.* Rectal bleeding.
6. Rapid, progressive course with fatal termination in an eight-week period.

Physical Findings:

1. Typical butterfly distribution of erythematous, scaly, atrophic lesion.
2. Cardiac impairment:

a. Systolic murmur.
b. Gallop rhythm.

3. General physical findings of a rapidly progressing, ravaging disease:
4. Papilledema.
5. Stomatitis and ulcerative pharyngitis.
6. Lymphadenopathy.

Laboratory Findings:

1. Indicative of marked bone marrow depression:

a. Severe anemia.
b. Leukopenia.
c. Thrombocytopenia.

2. Renal damage (though not marked).
3. Persistently negative blood cultures until a terminal bacteremia.
4. Electrocardiographic changes suggestive of pericarditis.

The salient features in the gross pathological findings can be summarized in this manner:

1. A generalized thickening of the serous membranes.
2. Extravasation of fluid into the body cavities.
3. Lymphadenopathy with necrosis.
4. Non-bacterial verrucous endocarditis of the Libman-Sacks type.

The microscopic findings revealed:

1. A generalized involvement of collagen and ground substance in a change which Klemperer et al.[8] term "fibrinoid degeneration."
2. Confirmation of the gross findings of lymph node necrosis.
3. Necrosis of the spleen.
4. Periarterial fibrosis in the spleen.
5. Changes in the glomerular tufts which might be termed minimal "wire looping."
6. A marked decrease in granulopoietic activity with a gelatinous-like degeneration in the bone marrow.

The clinical and laboratory findings, the course of the disease, plus negative evidence as regards other entities, and finally confirmation by pathological examination would seem to warrant the diagnosis of acute disseminated lupus erythematosus.

Comment

The definition "acute disseminated lupus erythematosus" would seem to us to be a most inaccurate and deceiving term. Most cases that are reported as acute lupus erythematosus disseminatus pursue a course varying from several weeks to several years with an approximate average duration of 18 months. The usual connotation of the word "acute" certainly, therefore, does not conform to the course of this disease.

The skin lesions are distinctly different in all respects from lupus vulgaris and, since a tuberculous etiology has been disproved to the satisfaction of most

students of the disease, it would seem that the term "lupus" has no place in the nomenclature.

"Disseminated" is definitely in good usage and employed advisedly; however, it is used as descriptive of a term (erythema) that is a part of the clinical picture, but certainly an inconsequential part. The skin lesions do fall into that group of skin lesions classified as the erythemas.

Many other terms have been suggested; however, none has been generally accepted as appropriate, which fact seems understandable when we take into account that we are attempting adequately to depict a disease of unknown etiology and characterized by such widespread and protean manifestations.

The present terminology is of such long-standing usage, however, that further attempts to change nomenclature would only add to the confusion.

The etiology of the disease continues to remain obscure and there is little to offer other than speculation and conjecture. The clinical features and course of clinical events vary greatly from case to case; however, in general the concept of a consistent clinical syndrome which permits diagnosis has been evolved.

The subjective and objective clinical findings may be divided into two phases; one the result of a severe intoxication and the other phase reflected by signs and symptoms incriminating such various organs and systems as are in that particular case involved by the pathological process. The different symptoms and signs may and do vary greatly in their severity and one or more may be lacking in the case in question. This fact seems easily understandable when one reflects that the pathological process may involve any organ or system of the body to a varying extent. Thus, it would seem feasible that the symptoms vary as do the site and extent of the pathologic lesions. Certain organs do appear to be sites of predilection and, in general, whatever the symptoms of the individual case, they seem to be grafted on a background of a severe toxic state.

The present case being reported as one of acute lupus erythematosus disseminatus with associated atypical verrucous endocarditis or Libman-Sacks syndrome brings forth an interesting point of discussion concerning the latter. This condition was first recognized and commented upon by Libman.[9] He observed what he termed an atypical verrucous endocarditis while in the course of his study of endocarditis, as early as 1911. This condition, although pathologically showing resemblance to the endocarditis of both rheumatic fever and subacute bacterial endocarditis, nevertheless differs in certain fundamental features. Libman-Sacks[7] in 1924 described in detail four cases of this condition which they considered as a distinct clinical entity.

Belote and Ratner[10] have recently questioned its existence as a nosologic entity. That this condition differs from the endocarditis of rheumatic fever and subacute bacterial endocarditis is doubtless universally recognized and such recognition is based on sound clinical and pathological evidence. However, its status as a distinct entity unto itself, which is likewise generally recognized, would seem to us to be open to doubt, or at least grave suspicion. When the clinical and pathological details noted in a case of acute lupus erythematosus disseminatus are compared with similar details from cases of atypical verrucous endocarditis, it is observed that they are fundamentally the same. The only constant difference is the occurrence of the endocarditis and at times the associated embolic phenomenon found in the Libman-Sacks syndrome.

Gross [11] compared the pathological changes in the hearts of 23 cases of acute lupus erythematosus disseminatus with those found in four cases of so-called Libman-Sacks disease with lupus erythematosus. Macroscopic changes were present in nine of the former group and microscopic changes in almost all of the cases. His conclusion was that the changes were characteristic of those found in the Libman-Sacks group, that in some instances they were identical, and that the two diseases were essentially the same and should be, therefore, under the one heading—namely, Libman-Sacks disease.

The skin lesions of the two conditions have been declared histologically alike by several competent observers. O'Leary,[12] in the discussion of Belote and Ratner's paper, states this fact. Likewise, it has been found in general that the pathology of these two conditions is fundamentally similar if not identical.

Gross [11] concluded the two conditions to be essentially the same but advocated that the condition of acute lupus erythematosus be considered under the single heading of Libman-Sacks disease. Ginzler and Fox [13] commented on the similarity between the two conditions as regards the clinical features. Rose and Pillsbury [14] state: "It seems beyond doubt that those cases described by Libman and Sacks with erythematous facial lesions were examples of acute lupus erythematosus disseminatus with visceral involvement." Belote and Ratner [10] report a case considered as an example of the Libman-Sacks syndrome and after careful study believe this entity should be classified as a sub-variety of the cases presented by Osler. We believe that the condition of acute lupus erythematosus disseminatus, Libman-Sacks disease, and at least some of the cases reported by Osler are all examples of the entity first appreciated by Kaposi and termed by him "lupus erythematosus discretus and aggregatus."

Certainly it would seem more plausible to consider that there have been cases of the so-called Libman-Sacks syndrome that prior to 1911 were overlooked because the case in question did not feature the endocardial changes or that, if present, they were missed because of lack of autopsy material or detailed microscopic study, than to believe that there is a newly discovered disease that is generally conceded to be fundamentally similar in all respects to an entity previously described by several competent workers.

Discussion of the Pathology

Klemperer, Pollack, and Baehr,[8] in 1941, discussed thoroughly and adequately the pathological findings in diffuse lupus erythematosus. Through their efforts, the pathologic criteria have been simplified and coördinated. Certain conspicuous changes have been described in the heart, spleen, blood vessels, serous membranes, and kidneys. These changes appear to show a common morbid process—an alteration affecting the connective tissue throughout the body, the so-called "fibrinoid degeneration." This change can affect any organ in varying degrees, accounting for the protean manifestations of the disease's clinical course and the absence of typical findings in some organs at postmortem examination. The serous membranes are usually thickened. There is often a pleuritis, pericarditis, and peritonitis of a fibrinous or fibrous type. Frequently effusions are present.

The heart is usually enlarged. The valves not infrequently present the picture of a Libman-Sacks endocarditis [7] with the histopathological picture varying from a simple sub-endothelial "fibrinoid degeneration" to hemorrhage,

necrosis, and thrombus formation. We feel that the Libman-Sacks atypical verrucous endocarditis is not a disease entity within itself, but rather a localized manifestation in the endocardium of the generalized alteration in the ground substance. Two possible mechanisms of pathogenesis present themselves: (1) The "fibrinoid degeneration" involving the capillaries supplying the valves causes an endarteritis with hemorrhage and necrosis and subsequent thrombus formation; (2) the "fibrinoid degeneration" and endothelial proliferation of the endocardium itself allow platelet deposition upon the surface with later organization and thrombus formation. The lesions in the case presented were of the "pyramidal-ridge" type.[15] Microscopically they showed an advanced type of lesion with necrosis, hemorrhage, and thrombus formation (figure 3). The blood vessels in the myocardium, as elsewhere, often show "fibrinoid degeneration" in their adventitial coats (figure 2).

"Periarterial fibrosis" is seen almost constantly in the spleen. Klemperer et al.[8] state, ". . . periarterial sclerosis found in nearly every case is so arresting that it must be considered specific." Kaiser,[16] however, recently describes these lesions in thrombocytopenia and other widely dissociated diseases as well as in disseminated lupus erythematosus. His conclusions, while against the specificity of this lesion, do not militate against its use as a positive diagnostic finding when used in conjunction with the clinical history and other pathological findings. Hemosiderosis, hyperplasia, and congestion are not unusual in the spleen. Our case showed marked and typical periarterial fibrosis (figure 4).

Enlargement and necrosis of the lymph nodes is generally described as a fairly consistent finding. Fox and Rosahn [17] found in their series of 280 cases that lymphadenopathy was present in 66.7 per cent. The histopathological picture was one of edema with engorgement and, not infrequently, necrosis. They felt that these lesions were ". . . suggestive of, but not specific for, the disease." Necrosis of the lymph nodes was a prominent feature in our case (figure 5).

The finding of "wire-loops" in the kidney has been described as being diagnostic of disseminated lupus erythematosus. This is considered to be fibrinoid degenerative changes in the glomerular arteriolar wall. Some cases show none of this distinctive change and we must consider that the kidney was spared the onslaught of the morbid process. Necrosis of the glomerular loops is also described. Glomerulonephritis has been reported in a number of cases and was present in our case, probably as a result of the terminal staphylococcic bacteremia. We found no evidence of fully developed "wire-loops" in our case, but felt that the changes present might be minimal changes. The liver has been reported as showing the picture of focal necrosis. No explanation has been advanced beyond a possible terminal bacteremia. Our case showed just such changes.

The brain often shows edema and a degenerative process. In our case there was an involvement of the blood vessel wall which resembles changes seen in periarteritis nodosa.

The bone marrow is usually described as normal or hyperplastic, even in those cases in which a leukopenia is seen clinically. The case presented showed a picture of marked granulopoietic depression with a peculiar gelatinous-like degeneration (figure 6). We feel that this is the reason for the lack of a leukocytic response to the bacteria and necrosis in the liver. Although tuberculosis as an etiological agent has been disproved,[9] it is occasionally seen at necropsy.

It is possible that in the past the necrosis which is often widespread in the lymph nodes has been mistaken for the caseous process of tuberculosis. There was no evidence of tuberculosis in our case.

SUMMARY

We have reported a case in a male which from its clinical signs and symptoms, course, and pathological findings, and lack of any other tenable diagnosis warrants the diagnosis of acute disseminated lupus erythematosus with atypical verrucous endocarditis (Libman-Sacks).

The findings as recorded and a review of the literature lead us to question the existence of a separate clinical entity termed the "Libman-Sacks syndrome" and to suggest that it is a local manifestation of an extensive and widespread pathologic process described previously as acute disseminated lupus erythematosus.

Acknowledgments. We are very grateful to Dr. B. Earl Clarke, Pathologist, and Dr. Elihu S. Wing, Chief of the Medical Staff, of the Rhode Island Hospital, Providence, R. I., for their help in the preparation of this paper.

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COMPARATIVE ELECTROCARDIOGRAPHIC CHANGES IN ANGINA PECTORIS AND CORONARY THROMBOSIS IN THE SAME PATIENT; REPORT OF A CASE *

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THE literature records a relatively small number of cases of fleeting electrocardiographic changes in the course of an attack of spontaneous cardiac pain.[1, 2, 3, 5, 6, 7, 8] Observations have been made to correlate these changes with those occurring following a coronary occlusion, both experimentally [4] and clinically.[9] An unusual opportunity presented itself to make observations relative to this matter in a patient with coronary artery disease, who while giving an account of the character of his recurrent attacks of precordial pain, developed the symptoms he was trying to describe. Four hours later he developed a more severe and persistent attack of pain which proved to be coronary thrombosis. Electrocardiograms were obtained during the fleeting attack of pain, two minutes after it had subsided, and at various intervals during and subsequent to the attack of coronary thrombosis. Such a sequence of events in one and the same patient recorded electrocardiographically is not a common experience. The record of this case is the subject of this report.

CASE REPORT

A 57 year old white male related that he had first experienced precordial pain on effort five years ago. These spells of pain recurred for several months, but since then he had been symptom free. On the morning in question he noted a recurrence of precordial pain on effort which lasted several minutes, and disappeared abruptly. While describing the attack he was suddenly seized with pain over his precordium. Advantage was taken of this opportunity to record an electrocardiogram while the pain persisted. Only three leads could be taken before the pain disappeared (figure A). S–T segment depression is noted in all three leads. About two minutes after he was relieved of his distress the three standard leads and an apex lead were repeated (figure B). All S–T segments have returned to the isoelectric line and a normal tracing is evident.

Examination of the patient at this time revealed no abnormal findings. His color was good. The pulse was of good quality. Regular rhythm was present, there were no murmurs, and the blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. Fluoroscopy revealed no abnormalities in the size and shape of the heart and aorta.

Four hours later, during the night, the patient was awakened from his sleep with severe precordial pain. This was more severe than the previous attacks, and more persistent. The heart sounds were poor, rhythm was regular, pulse was 88 per minute. By morning his pain had abated somewhat. An electrocardiogram taken at this time (figure C) shows depression of the S–T segment in Leads II and III. The ensuing course followed the pattern of an acute myocardial infarct. The temperature reached the high level of 102° F. within the next several days and returned to normal on the eighth day. The blood pressure fell to 108 mm. Hg systolic and 80 mm. diastolic, and returned to 130 mm. systolic and 90 mm. diastolic at the end of the fourth week. He exhibited an increased sedimentation rate until after the fifth week. Serial electrocardiograms are presented to illustrate the changing pattern (figures D, E.).

* Received for publication July 24, 1944.
From the Cardiac Service of Dr. Harry Gold, The Hospital for Joint Diseases.

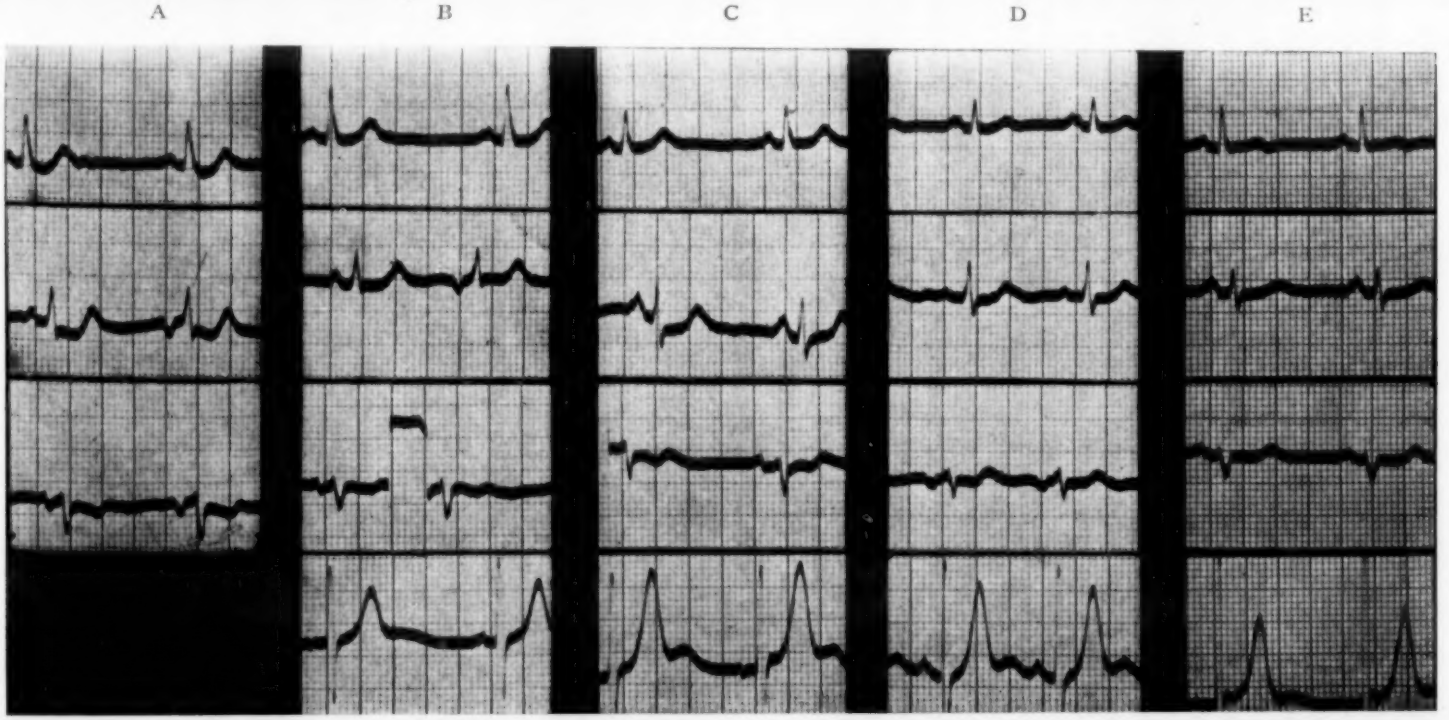

FIG. 1. *A:* Three standard leads taken during a spontaneous attack of angina pectoris. Shows depression of the S–T segments in all leads. *B:* Three standard leads and an apex lead taken after relief from the anginal attack. Shows return of the S–T segments to the isoelectric line. *C:* Electrocardiogram taken eight hours after an attack of coronary thrombosis; approximately 12 hours after figure B. Shows S–T segments in Leads II and III depressed below the isoelectric line. *D* and *E:* Serial electrocardiograms taken the following day and 13 days later respectively. This illustrates the changing pattern as seen in coronary occlusion, rather than the return to normal as seen in figure B following the recovery from the anginal attack.

Comment

The electrocardiographic changes occurring during the course of functional cardiac pain showed the same pattern as those in the early phases of coronary thrombosis, which occurred four hours later. It is noteworthy to point out, however, that the changes were more extensive during the pain of the functional episode than during the terminal phase of the pain due to the organic episode, since S–T segment changes occurred in all three standard leads during the former, and only in Leads II and III during the latter. One can only speculate concerning the significance of these differences. The initial electrocardiogram was taken during the severe pain of the anginal attack and may, therefore, be indicative of the generalized reflex myocardial ischemia which takes place, although it is fleeting. On the other hand, the electrocardiogram taken following the coronary thrombosis was taken after the severe pain had subsided, which may in turn indicate a lesser degree of reflex spasm, and, therefore, a lesser degree of generalized myocardial ischemia.

One may also emphasize the fact, to which attention has been called repeatedly in the literature, and as clearly demonstrated in this case, that a normal electrocardiogram does not preclude advanced coronary artery disease. This patient showed a normal electrocardiogram two minutes after one demonstrating severe myocardial ischemia, and four hours before a coronary thrombosis.

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EQUINE INFECTIOUS ANEMIA TRANSMITTED TO MAN *

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IN his recent book, titled "Diseases Transmitted from Animals to Man" (1941), Thomas Hull [1] writes: . . . "equine infectious anemia has never been known to infect man." The purpose of this report is to demonstrate that this statement is no longer valid. It is not difficult to recognize this virus disease if the possibility of its occurrence be remembered. It may be expected that other cases will soon be discovered among patients with aplastic anemia of unknown origin if the method of examination described in this article be applied. This expectation is based on the following facts: *a.* There is a large number of infected horses and mules in the United States and elsewhere. The disease in horses tends to occur in certain large areas. In the United States, according to Hagan [2] (1943) many horses in the northern and western states and many mules in the Mississippi Delta region die from this disease. *b.* Insects, which are well-known "blood-suckers" in man, are at the same time transmitters of equine infectious anemia. *c.* Some forms of aplastic anemia of unknown origin are strikingly similar to the anemia which was observed in the case described below.

CASE REPORT

The patient, who was a professor of pathology and hematology at a School of Veterinary Medicine, had himself made the diagnosis of infectious anemia. He was convinced that physicians knew much less about the disease than he did. Therefore, he had refused all aid and examinations by physicians. However, the author succeeded in persuading him that a comparison of his symptoms and signs with those associated with certain anemias, described in man, might add significantly to our knowledge of these diseases. The patient consented to be examined, but under these circumstances the author could not perform certain examinations (e.g., bone marrow studies) which the patient considered to be unnecessary.

The patient, a man 45 years of age, was a veterinarian who often came in contact with horses suffering from equine infectious anemia. The patient was never sick before this, and his family history was irrelevant. His chief complaint was weakness. The present illness began two years previously when a skin eruption which the patient called a "herpetiform exanthema" appeared in the umbilical region. It soon disappeared. At that time diarrhea alternating with constipation occurred. A few weeks after the onset of the disease a slight edema appeared, extending over the whole body but most evident in the eyelids. There was no albuminuria. Between the attacks there were short intervals when the patient felt well. However, constant weakness and pallor of the skin developed. Severe headaches were frequent and were localized usually in the occipital region. Now and then fever occurred, but was never of a high grade. After a few months the intervals of relative well-being returned and were longer than before, but the recurring attacks were just as severe.

Laboratory findings: The urine revealed no pathological findings. The blood was examined on numerous occasions by the patient himself. Hemoglobin was approximately 30 volumes per cent (Sahli), that is about 4.3 gm. per cent. The num-

* Received for publication January 10, 1944.

ber of red cells per cu. mm. was about two millions. The mean corpuscular hemoglobin was 23 and the color index 0.8. Normoblasts and megaloblasts were never found. Poikilocytosis and anisocytosis were always present. The number of leukocytes varied from 1800 to 2600 per cu. mm. The differential count revealed no abnormalities except a relative lymphocytosis. The number of the platelets was within normal limits, but many were so-called "giant platelets." This is perhaps of diagnostic importance. The patient had an intestinal hemorrhage during only one of the exacerbations. Between the attacks no hemorrhage occurred. The following negative findings may be mentioned. The lungs and heart showed no abnormal findings, except anemic systolic murmurs over all the ostia. The blood pressure was always within normal limits. The liver and spleen were not enlarged. Jaundice was absent and there was no increased loss of urobilin and urobilinogen. There were no aphthae on the tongue. There was no tenderness on pressure over the sternum or other bones.

Physical examination: This revealed no data of importance which have not been mentioned. In order not to present a confused picture, it seemed better to mention in this article only the symptoms and laboratory findings observed during the peak of the disease because only these enable the examiner to make the right diagnosis.

From the onset of the symptoms—as mentioned above—the patient had made the diagnosis of equine infectious anemia in himself because his symptoms were similar to those observed in infected horses. He was convinced that he had to die from this disease which he called by the older name "pernicious anemia." He saw this outcome in the majority of the infected horses. The proof that his diagnosis was correct was demonstrated by the following test which is used regularly in horses. The patient injected 1 c.c. of his blood intravenously into a young strong horse. The animal died from equine infectious anemia. This crucial test was repeated with the same result in two other young healthy horses. He carried out these tests with filtered and unfiltered blood with identical results. This excluded other diseases not caused by a virus. For nearly two years the poor condition of the patient remained unchanged. At the beginning of the third year, during which the author examined the patient, an amelioration of the disease appeared. The first sign was that the intervals between the attacks became longer. Of great importance was the fact that a horse, injected with the patient's blood, remained healthy. This was repeated in other horses with the same result. The reason this repetition was necessary is the existence of "healthy" equine carriers which will be discussed later.

However, in spite of the fact that his blood was negative, his prognosis remained unfavorable because he knew cases in horses which were apparently healthy and whose blood remained negative during long periods, yet after 10 years or more new attacks developed in one of which the animal died.

From the blood picture, described above, it is obvious that the patient had an aplastic type of anemia which involved the myeloid and erythrogenic tissues but not the platelets. Such forms of anemia are known to occur in man. In the hematologic literature this form of anemia in man is described under the heading: "Atypical Forms of Aplastic Anemia." One of these forms was called by Downey [3] in 1938: "Aplastic Anemia without Thrombocytopenia." Giant platelets are found in human blood in chronic infections. They may become so large that they are confused with flagellates. This happened to the author as he saw these platelets for the first time. This possibility should be remembered in future cases. There is certainly sufficient reason to carry out an inoculation of a horse with the blood of a patient who is suffering from "aplastic anemia without thrombocytopenia" with giant platelets. If it is negative a second horse should be inoculated for reasons given below. However, even if thrombocytopenia

is present with or without giant platelets, one should carry out this test because in horses there are variations which may occur also in man. In the chronic form of aplastic anemia in man hemorrhage is rare, in sharp contrast with the well-known occurrence of hemorrhage in the acute form. This is in accordance with this patient's symptoms.

Since this virus infection has to be added to the "human diseases" it is of importance to know what has already been discovered concerning this disease, and also to know the gaps in our knowledge which still have to be filled in. For this purpose the author used Hagan's Infectious Diseases of Domestic Animals,[2] Runnells' Animal Pathology,[6] and an article of C. Stein et al.[7]

In 1904 the French investigators Carré and Vallée discovered that the etiologic agent of this disease was a filtrable virus. They showed that filtrates, passed through Berkefeld filters, could infect other horses. The virus was found in blood, urine and feces. Its length is between 18 and 50 millimicra. It is very resistant to disinfectants, freezing, and desiccation, and is little affected by age. Dried blood retains virulence for several months, if protected from sunlight. Of great importance for the possibility of an infection in man is the fact that the disease is spread principally through the agency of insects. The chief offenders are the blood-sucking common stable fly, *Stomoxys calcitrans* and the mosquito *Anopheles maculipennis*. It is probable that the *Anopheles quadrimaculatus*, the malaria-transmitter in the United States, also transmits infectious anemia. This is all the more probable since this infection can be transmitted mechanically by the bite. Scott showed that infection in horses could be produced by a single prick with a hypodermic needle which was contaminated by pricking an infected horse. There is some evidence that horses can also be infected by feeding from the same floor or from common containers. However, the principal transmitters are insects. There are no reports of successful cultivation of the virus in artificial media. Therefore, the only way to detect the many apparently healthy virus-carriers among horses is to inoculate their blood into other horses. However, the fallacy in this experiment is that the selected animal may already be a carrier and, therefore, may not react. For this reason, if the first test is negative, it is necessary to inoculate a second horse in order to make the chance of error smaller. The discovery of a suitable artificial culture medium would be of priceless value, not only for the diagnosis in horses, but also for the routine examination of blood in human aplastic anemia. Here lies an open field for a bacteriologist.

If an inoculated test-horse is susceptible, it presents fever usually within 15 to 30 days. The most constant findings are a rapid decrease in hemoglobin and red cells, an increase in the sedimentation rate and in the plasma globulins. The blood changes are more or less variable, as already mentioned.

It can be expected that after this war, there will be a further spread of the disease in horses. After every war this phenomenon has occurred. Horses are assembled, during wars, from many areas. The return of horses to civilian life is likely to set up new foci.

In horses there is an acute, subacute and chronic form of infectious anemia. In the acute form death may occur within a few days. The subacute form may lead to death within three months. Both forms may go into the chronic form which is often interrupted by acute exacerbations, during any of which death may occur. The blood usually remains infectious, but may become temporarily

free from the virus. Some investigators believe that recovery in horses never occurs, but this conception is incorrect according to others.[4] How treacherous this disease is, at least in horses, is shown by the history of a horse described by Schalk and Roderick.[5] This horse was used as a test-animal. It had several acute attacks during the first three years, but then lived apparently in good health for 14 years. Every year the blood was inoculated into another horse. All of these inoculated horses, except one, developed the disease. Then suddenly the horse died in an acute attack.

The results of inoculations of rabbits and birds have been unreliable, because these animals often seem to be immune. Means of immunization have not yet been developed, in spite of many attempts. The problem of therapy is unsolved.

Summary and Conclusions

1. Equine infectious anemia can be transmitted to man.

2. The blood of patients with the so-called idiopathic aplastic anemia should be inoculated in horses in order to diagnose this disease in man. This test should not be considered too expensive because it is probably harmless for the animal if the patient does not have infectious anemia, and it is of great diagnostic importance if the horse develops the disease. It can easily be done in the larger veterinary institutions because in such places this inoculation is a routine test for the diagnosis of the disease in horses. (The author has received a letter from the Veterinary Institution in Washington, D. C., stating that blood from a suspected case would there be injected into a healthy horse.)

3. The probability that cases will soon be detected in man is emphasized, especially if adequate culture media for the virus are found. This opinion is supported by three facts: (*a*) The large number of infected horses and mules. (*b*) The insects which transmit the disease among horses are the same which are known to bite man. Merely contact of the sting contaminated with infected blood is sufficient for the transmission of the disease. (*c*) A description of the anemia which the patient had can be found in all textbooks of medicine under the heading "Idiopathic Aplastic Anemia" which is not a rare disease. At the present time the only reliable method of making the diagnosis of this disease is the inoculation of horses with blood of the patient.

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EDITORIAL

METHODS OF ADMINISTERING PENICILLIN

THE inactivation of penicillin by the gastric juice, which renders it ordinarily ineffective by mouth, and its rapid excretion in the urine when given by parenteral injection, have given rise to troublesome technical difficulties in its administration. Thus far the most efficient method of maintaining an effective concentration in the blood and the most economical as far as the wastage of drug is concerned is the continuous intravenous drip. The practical disadvantages of this procedure are obvious and have stimulated many attempts to devise some simpler method of administration.

Subcutaneous injections are irritating and painful, and absorption has been reported to be irregular and uncertain.

After intramuscular injections absorption is rapid, reaching a maximum level which is highly effective after from 30 to 60 minutes, but it then falls off rapidly, and if ordinary doses are used (15,000 to 20,000 units), before the end of three hours the concentration often falls below the effective range. For susceptible organisms like the gonococcus, the pneumococcus and the hemolytic streptococcus, this is usually an effective procedure, although the necessity of continuing the injections day and night without interruption is a strain on the patient as well as the medical personnel. It is not adequate for the more resistant organisms such as the staphylococcus and the *Streptococcus viridans* in bacterial endocarditis.

Doubling the dose of penicillin injected prolongs somewhat the period during which an effective concentration in the blood is maintained, perhaps an hour. The alternatives are to reduce the interval to two hours, or to institute a continuous intramuscular drip. This can be done by dissolving the total daily dose of penicillin in 500 c.c. of salt solution and maintaining a flow at a rate of six to eight drops a minute. It maintains an effective concentration in the blood and is economical of penicillin. It is often painful, however, and is usually more objectionable to the patient than an intravenous drip, and except for freedom from thrombosis it shares most of the drawbacks of the latter procedure.

Attempts to improve the technic of intramuscular injections have been designed either to slow the rate of absorption or to lessen the rate of excretion in the urine.

In 1944 Raiziss [1] found that penicillin suspended in oil was more slowly absorbed and an effective concentration in the blood was maintained longer than when injected in aqueous solution. Romansky and Rittman [2] obtained

[1] RAIZISS, G. W.: Penicillin in oil suspension. Bacteriostatic and spirocheticidal agent, Science, 1944, c, 412–413.

[2] ROMANSKY, M. J., and RITTMAN, G. E.: Penicillin: prolonged action in beeswax-peanut oil mixture; single injection treatment of gonorrhea, Bull. U. S. Army Med. Dept., 1944 (Oct.), 43–49.

effective levels for six to 10 hours by injecting 100,000 units suspended in 3 per cent beeswax in peanut oil. They reported curing gonorrhea in a number of cases by a single injection.

Trumper and Hutter [3] utilized ice packs applied to the site of injection. In nine of 10 cases of gonorrheal infection they were able to maintain effective blood levels for six to 12 hours, and obtained clinical cure after a single injection of 50,000 or 100,000 units of penicillin. They usually applied the packs for two hours before the injection and for six or 12 hours following it.

Fiske, Foord and Alles [4] employed adrenalin to slow absorption. After demonstrating that penicillin was stable in dilute solutions of adrenalin and that in rabbits it prolonged the period during which an effective blood level was maintained after a single subcutaneous or intramuscular injection, they tested the mixture on seven human subjects. By dissolving 50,000 units of penicillin in 4 c.c. of 1–50,000 dilution of adrenalin solution, they approximately doubled the time during which an effective blood level (0.039 unit per c.c. or more) was maintained (about three hours as compared with one and one-half to two hours after injections of penicillin in salt solution).

Parkins et al.[5] attempted to combine these two principles by adding penicillin powder to a 6 per cent or 20 per cent gelatin solution containing 0.025 or 0.005 per cent of neosynephrine. In experiments on dogs and also in a few human cases they found that the use of either gelatin or neosynephrine prolonged the effect somewhat (to about four hours), but the use of both gave more satisfactory results. In human cases, following an intramuscular injection of 50,000 units, a significant blood level (0.02 to 0.08 unit per c.c.) persisted for six to eight hours. If this finding is confirmed, it should be possible in some cases to reduce the number of intramuscular injections per day from at least eight to three or four.

The early observation that high levels of penicillin were maintained in the blood for several hours in patients with renal insufficiency [6] led others to seek artificial means of slowing its excretion in the urine. Rammelkamp and Bradley [7] noted that excretion was delayed following diodrast injection. Beyer et al.[8] found that the addition of 6 per cent of sodium para-aminohippurate to penicillin solution on intravenous injection increased the plasma content of penicillin two to five times, depending upon the concentration of hippurate attained in the blood. No untoward effects were noted in short

[3] Trumper, M., and Hutter, A. M.: Prolonging effective penicillin action, Science, 1944, c, 432–434.

[4] Fiske, R. T., Foord, A. G., and Alles, G.: Prolongation of penicillin activity by means of adrenalin, Science, 1945, ci, 124–125.

[5] Parkins, W. M., et al.: Maintenance of the blood level of penicillin after intramuscular injection, Science, 1945, ci, 203–205.

[6] Rammelkamp, C. H., and Keefer, C. S.: Absorption, excretion and distribution of penicillin, Jr. Clin. Invest., 1943, xxii, 425–437.

[7] Rammelkamp, C. H., and Bradley, S. E.: Excretion of penicillin in man, Proc. Soc. Exper. Biol. and Med., 1943, liii, 30–32.

[8] Beyer, K., et al.: The effect of para-aminohippuric acid on plasma concentration of penicillin in man, Jr. Am. Med. Assoc., 1944, cxxvi, 1007.

(12 hours) experiments in human cases. The hippurate is regarded as "competing" with the penicillin for excretion in the renal tubules.

Bronfenbrenner and Favour [9] studied the effect of administering benzoic acid by mouth (2.5 gm. every four hours) on the rate of excretion and blood level of penicillin after intramuscular injections of 20,000 units. With a liberal fluid intake, this exerted only a moderate effect, but if at the same time fluid was restricted to 1000 to 1500 c.c. a day, and salt to 3 gm. a day, the plasma concentration at 30 and 60 minute intervals was increased eight fold, and the duration of the high blood level prolonged to more than two hours.

Attempts have also been made to devise an effective procedure for oral administration. Penicillin is absorbed quite readily after it reaches the duodenum, but is inactivated by the acid gastric juice. It was noted early that in cases with achlorhydria, penicillin appeared in the blood after mouth administration. To protect the penicillin from this destructive action it has been administered in enteric coated capsules and in conjunction with various acid-neutralizing substances. The results obtained by the use of the ordinary enteric coatings have in general been inconstant and unsatisfactory.

Libby [10] suspended powdered sodium and calcium salts of penicillin in cottonseed oil and administered this in gelatin capsules. Following a single dose of 90,000 units the blood level ranged from 0.03 to 0.05 unit per c.c. for four hours. Two subsequent doses of 20,000 units at three hour intervals maintained this level for eight hours. The best results were obtained if the penicillin was given when the stomach was empty.

Charney et al.[11] administered 7 gm. of trisodium citrate or 2.5 gm. of disodium phosphate with penicillin by mouth, and determined the amount excreted in the urine during the subsequent six hour period as an index of absorption. When given after meals, there was on the average a substantial increase in the percentage of penicillin recovered in the urine as compared with the controls (from about 2 per cent to 20 per cent). The results with sodium bicarbonate, calcium carbonate and aluminum hydroxide in a few experiments were less satisfactory. When administered fasting, more penicillin was excreted by the controls and the increase obtained by the administration of the antacids was at best slight. Furthermore, individual variations were large.

McDermott et al.[12] followed the blood penicillin levels in a group of subjects after single oral doses of 315,000 units administered (1) in aqueous solution, (2) in aqueous solution preceded by three doses of 4 gm. of magnesium trisilicate at one hour intervals, (3) in corn oil, and (4) in 4 per cent beeswax in peanut oil. Following this large dose, after 30 and 60

[9] Bronfenbrenner, J., and Favour, C. B.: Increasing and prolonging blood penicillin concentrations following intramuscular administration, Science, 1945, ci, 673–674.

[10] Libby, R. L.: Oral administration of penicillin in oil, Science, 1945, ci, 178–180.

[11] Charney, J., et al.: Urinary excretion of penicillin in man after oral administration with gastric antacids, Science, 1945, ci, 251–253.

[12] McDermott, W., et al.: Oral penicillin, Science, 1945, ci, 228–229.

minute intervals, effective blood levels in the range of 0.6 to 0.8 unit per c.c. were recorded for all the procedures, without a significant difference between them, although the levels at the two hour interval were better sustained after the oil suspensions. They state that "qualitatively similar results" were obtained with doses of 100,000 and 50,000 units, and conclude that blood levels comparable to those following intramuscular injections can be obtained by oral administration of a dose five times as large.

Krantz, Evans and McAlpine [13] reported more successful results by the administration of 100,000 units combined with 3 gm. of basic aluminum aminoacetate. The average serum concentrations in 12 cases ranged from 0.39 unit per c.c. at two hours, 0.68 unit at three hours, 0.37 unit at five hours, to 0.17 unit at seven hours. There were large individual variations.

Burke et al.[14] also reported favorable results following the administration of penicillin in gelatin capsules hardened by immersion in formaldehyde and alcohol, 30 minutes after the ingestion of two tablets of aluminum hydroxide. These capsules resisted the action of gastric juice in vitro for one to two hours. Following 200,000 units, high blood levels were obtained after one-half hour and remained at an effective level for four to five hours. This level was maintained for about three hours after 100,000 units. This "compared favorably" with the average levels following 40,000 units intramuscularly.

Rectal administration has been regarded as impracticable because of destruction of penicillin by colon bacilli. Loewe et al.,[15] however, have obtained detectable concentrations in the blood of 12 of 14 cases following the administration of large doses (300,000 to 1,000,000 units) of sodium penicillin in cocoa butter suppositories. The results were variable, and in most cases the blood levels were low, but a level of at least 0.012 unit, the minimum effective against the most susceptible organisms, was maintained for six hours or more in half the cases tabulated. Manifestly the method must be greatly improved before it will have practical value.

Barach et al.[16] have reported promising results in the treatment of subacute and chronic infections of the lungs and bronchi by inhalations of penicillin aerosol. In these cases the concentration of penicillin in the blood usually ranged from 0.01 to 0.04 unit, and in one case to 0.18 unit, and could be increased by deep breathing to 0.4 unit. It seems quite possible that this may prove to be the best method of treating such conditions in which a high concentration of penicillin in the mucous membranes is presumably desirable. It seems unlikely that it would be practicable in other types of infection.

[13] KRANTZ, J. C., JR., EVANS, W. E., JR., and MCALPINE, J. G.: Oral penicillin with basic aluminum aminoacetate, Science, 1945, ci, 618–619.

[14] BURKE, F. G., ROSS, S., and STRAUSS, C.: Oral administration of penicillin, Jr. Am. Med. Assoc., 1945, cxxviii, 83–87.

[15] LOEWE, L., et al.: Penicillin by rectum, Jr. Am. Med. Assoc., 1945, cxxviii, 18–19.

[16] BARACH, A. L., et al.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis, and lung abscess: preliminary report, Ann. Int. Med., 1945, xxii, 485–509.

The reports which have been reviewed are all preliminary in nature, and the number of observations on which they are based is far too small to warrant any definite conclusions. Certain tentative ones, however, may be permissible.

Thus far no method except continuous intravenous or intramuscular drip can be depended upon to maintain continuously the relatively high blood concentration needed in infections with the more resistant organisms. Intramuscular injections of moderate doses of penicillin in aqueous solutions can not be depended upon to maintain a really effective blood level for more than two hours, although in many cases this may persist three hours. Doubling the dose of penicillin delays the fall in the blood level somewhat, but it is wasteful of drug, since a relatively large excess of penicillin is required to secure a comparatively slight delay. It is doubtful whether anything is gained from the transient excessively high levels reached soon after such injections.

It seems probable that some procedure designed to slow absorption may be so perfected that an adequate blood level can be maintained for at least eight hours after a single intramuscular injection. The most promising appear to be the use of oil or gelatin as a vehicle, in association with a persistent local vasoconstrictor. Procedures designed to retard excretion by the kidney require a great deal more study before their general use is justified.

The oral administration of penicillin is still in the early experimental stage, and at present it can not be depended upon in treating an infection of any gravity whatsoever. This preliminary work offers a definite hope that some effective procedure may be found, perhaps the use of an oil vehicle, a suitably hardened capsule, an effective antacid, or a combination of such measures. Thus far, however, it is little more than a hope. One point which stands out clearly is the great variability in the response of different individuals. Even those procedures which seem most promising on the basis of average values fail in certain cases. Large doses are required, at least two to five times that for intramuscular injection, and these would have to be repeated at least once in three or four hours to warrant any expectation of effectiveness. The indiscriminate dispensing of penicillin for oral use in combination with some antacid, which now threatens to come into vogue, is at present premature and ill advised, and is likely to prove highly disappointing.

Fortunately the primary toxicity of penicillin is negligible, and there is little risk of direct injury to the patient from such use. Penicillin also has much less tendency than the sulfonamides to render organisms resistant when it is administered intermittently and in inadequate doses. There is evidence, however, that certain individuals may become sensitized to penicillin. Cases of contact dermatitis have been reported, as well as generalized reactions during a second course of treatment.[17] The frequency of such reactions is not yet known, but this may prove an additional reason for avoiding the unnecessary or ineffectual administration of this drug.

[17] CRIEP, L. H.: Allergy to penicillin, Jr. Am. Med. Assoc., 1944, cxxvi, 429.

REVIEWS

Radiologic Examination of the Small Intestine. By Ross Golden, M.D. 239 pages; 26 × 18 cm. 1944. J. B. Lippincott, Philadelphia. Price, $6.00.

The smallness of this book attests to the lack of knowledge of the diseases of the small bowel. It is apparent that this segment of the gastrointestinal tract has received less study than the remaining portions, which is perhaps due to its being more silent in its diseases than the rest. With the exception of complete obstruction of the small intestine, the symptoms produced by a pathological small bowel are far less dramatic than those of the stomach or colon.

On perusing this volume, it becomes evident that there is still much to be desired in roentgen examination of the small intestine. Dr. Golden presents very clear roentgenograms of the inflammatory, nutritional and emotional changes that occur in the small bowel. The immediate impression is that they are indistinguishable from one another.

The chemical mediator theory is discussed, together with case histories and the results of therapy based on this theory. But this, too, is still indefinite and calls for much further research.

The book is well illustrated and is very readable. The data included should act as a stimulus for further work on the small bowel. This volume could scarcely be classified as a reference one, since major portions of the information are inconclusive in nature.

D. J. B.

Savill's System of Clinical Medicine Dealing with the Diagnosis, Prognosis, and Treatment of Disease for Students and Practitioners. Twelfth Edition. Edited by E. C. Warner, M.D., F.R.C.P. 1168 pages; 22 × 15.5 cm. 1944. The Williams and Wilkins Company, Baltimore. Price, $9.00.

The character of the present edition is unchanged from that of the first editions, which were planned by Dr. Thomas Savill and subsequently produced under the editorship of Dr. Agnes Savill. The changes are concerned mostly with modernization of methods of treatment and newer laboratory tests of established value. The greatest change has been in extracting "Psychological Disorders" from "Diseases of the Nervous System" and devoting a new chapter to this growing specialty.

The special value of this book is in its plan of organization, which is based on the presenting symptoms of disease. Each chapter is divided into three parts: (1) the symptoms the patient presents and the differential diagnosis; (2) the physical and clinical signs; and (3) a classification of diseases of that anatomical region with prognosis and treatment. Treatment is the weakest aspect of this edition, as it was in the previous ones. Some of this inadequacy may be due to the delays in publication during the rapid therapeutic advances of wartime. The sulfonamides are tabled briefly and the reader is cautioned against advising eggs, meat, and onions during their administration because of cyanosis due to sulf-hemoglobinemia and met-hemoglobinemia. Some of the inadequacy may be apparent rather than real and due to a difference in conventional therapeutic ideas in England and America, such as the value of morphine in asthma and of procedures of venesection and leeching in pneumonia with right heart strain; or, as in the case of "toxic adenoma (secondary Graves' disease)", the reader is advised against the use of iodine because it makes the condition worse.

The book is valuable to undergraduate and graduate clinicians who wish fundamental information in a readily available form. Symptoms which are classified in

other sections are described briefly and cross references are complete. It is because of this excellent organization that this book is superior to the usual text of differential diagnosis.

M. V. P.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Index of Differential Diagnosis of Main Symptoms. Sixth Edition. By Various Writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D.Oxon., F.R.C.P. Assisted by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P. 1128 pages; 26 × 17 cm. 1945. Williams and Wilkins Company, Baltimore. Price, $17.00.

Some Fundamental Principles of Metabolism. By L. H. NEWBURGH, M. W. JOHNSTON, and J. D. NEWBURGH. 62 pages; 28 × 22 cm. 1945. J. W. Edwards, Ann Arbor, Michigan. Price: Paper bound $1.25; cloth bound $1.75.

Text-Book of Pharmaceutical Chemistry (Bentley and Driver). Fourth Edition. Revised by JOHN EDMUND DRIVER, M.A. (Cantab.), Ph.D., M.Sc. (Lond.), F.R.I.C. 644 pages; 22.5 × 14.5 cm. 1945. Oxford University Press, New York. Price, $7.50.

The Basis of Clinical Neurology. Second Edition. By SAMUEL BROCK, M.D. 393 pages; 23.5 × 16 cm. 1945. Williams and Wilkins Company, Baltimore. Price, $5.50.

Men Under Stress. By ROY R. GRINKER, Lt. Col., M.C., and JOHN P. SPIEGEL, Major, M.C., Army Air Forces. 484 pages; 24 × 16 cm. 1945. The Blakiston Company, Philadelphia. Price, $5.00.

The Bacterial Cell in Its Relation to Problems of Virulence, Immunity and Chemotherapy. By RENÉ J. DUBOS. With an Addendum by C. F. ROBINOW. 460 pages; 22 × 14.5 cm. 1945. Harvard University Press, Cambridge, Massachusetts. Price, $5.00.

A Synopsis of Medicine. Eighth Edition. By SIR HENRY LETHEBY TIDY, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.). 1215 pages; 19 × 13 cm. 1945. Williams and Wilkins Company, Baltimore. Price, $7.50.

Common Ailments of Man. Edited by MORRIS FISHBEIN, M.D. 177 pages; 20.5 × 14 cm. 1945. Garden City Publishing Company, New York City. Price, $1.00.

Clinical Atlas of Blood Diseases. Sixth Edition. By A. PINEY, M.D., M.R.C.P., and STANLEY WYARD, M.D., F.R.C.P. 138 pages; 20.5 × 13.5 cm. 1945. The Blakiston Company, Philadelphia. Price, $5.00.

COLLEGE NEWS NOTES

New Life Members

Since the publication of the last issue of the Annals of Internal Medicine, the following Fellows of the College have become Life Members (listed in the order of subscription):

Dr. Hugo O. Altnow, Minneapolis, Minn.
Dr. Harold C. Ochsner, Indianapolis, Ind.
Dr. Harry Plummer Ross, Richmond, Ind.

Enlistments and Discharges, A. C. P. Members

Dr. Timothy F. Breuer, F.A.C.P., Hartford, Conn., has been commissioned a Lieutenant Commander in the U. S. Naval Reserve. This brings the total number of College members who have entered upon military duty to 1,864.

The following members of the College have been honorably discharged:

Leroy E. Burney, Senior Surgeon, USPHS—Indianapolis, Ind.
M. Coleman Harris, Lieutenant Commander, (MC), USNR—New York, N. Y.
Meredith B. Hesdorffer, Past Assistant Surgeon, USPHS—Minneapolis, Minn.
Roy Herbert Holmes, Major, (MC), AUS—Muskegon, Mich.
W. Byrd Hunter, Lieutenant Colonel, (MC), AUS—Huntington, W. Va.
John L. Kantor, Colonel, (MC), AUS—New York, N. Y.
Charles H. Watkins, Captain, (MC), USNR—Rochester, Minn.

Oral Examinations, American Board of Internal Medicine

Oral examinations by the American Board of Internal Medicine will be held in San Francisco, October 15–16–17. They are intended primarily for candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming. The closing date for registering is September 1. Write for application form to the American Board of Internal Medicine, 1 West Main St., Madison 3, Wisconsin.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Books

"Rypins' Medical Licensure Examination," Fifth Enlarged Edition, completely revised under the editorial direction of Dr. Walter L. Bierring, F.A.C.P.

Reprints

Samuel M. Alter, F.A.C.P., Los Angeles, Calif.—2 reprints.
Harold R. Carter (Associate), Denver, Colo.—2 reprints.
Irving Gray, F.A.C.P., Brooklyn, N. Y.—5 reprints.
Harold J. Harris, F.A.C.P., Lieutenant Commander, (MC), USNR—3 reprints.
Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—1 reprint.
Bruce R. Powers, F.A.C.P., Knoxville, Tenn.—1 reprint.
Horace K. Richardson, F.A.C.P., Baltimore, Md.—1 reprint.
Mitchell A. Spellberg (Associate), Major, (MC), AUS—7 reprints.
Leon H. Warren, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.

Dr. Carl J. Wiggers, F.A.C.P., Director of the Department of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio, presented a copy of the "Collected Papers from The Department of Physiology of Western Reserve University School of Medicine," Vol. XI.

Report from the Office of The Surgeon General, U. S. Army

Anniversary of the Army Medical Department

The Army Medical Department celebrated its 170th anniversary on July 27 of this year with the realization that it has grown into the largest organization of the kind ever known and that it is giving this nation's army the best medical care that soldiers have ever received. From its inception in 1775, shortly after General George Washington became Commander-in-Chief of the Continental Army, until the present day the Army Medical Department has made steady progress in military medicine; it has made scientific discoveries that have benefited all mankind, but never has its progress in both of these categories been so rapid as in recent years.

Colonel Pincoffs on Temporary Duty in Washington

Colonel Maurice C. Pincoffs, F.A.C.P., of Baltimore, Md., has been on temporary duty this month at the Office of The Surgeon General after three years overseas. He went over as Commanding Officer of the 42nd General Hospital, University of Maryland Affiliated Unit in the Southwest Pacific Area, then served as Chief Medical Consultant to The Chief Surgeon, United States Forces in the Far East, and most recently has been Health Officer of Manila. He addressed The Surgeon General's semimonthly meeting on the difficult task of reëstablishing a public health service in Manila and bringing it up to a functioning level.

The Japs left Manila without lights, water, sewage facilities, street-cars, telephones or mail service, he pointed out. In addition to the lack of public utilities there was a shortage of civilian medical supplies. There were large civilian casualties and most of the hospitals had been destroyed, yet because of the splendid work of American medical units and available Filipino personnel, he said, the provisional health department was functioning smoothly within six weeks.

Colonel Pincoffs, who is on leave from the University of Maryland where he has been Head of the Department of Medicine since 1922, has been honored for his services in two wars. His awards include the Croix de Guerre, the Silver Star with Palm, the Distinguished Service Cross and the Legion of Merit. He expects to return to the Pacific when his tour of duty here is completed.

Adequate Safeguards

Less exotic disease has been introduced into the United States by returning soldiers than medical officers anticipated and though safeguards now in effect should be continued, no new steps are necessary. This was the consensus of the Interservice Committee of the Army and Navy Medical Department and Public Health Service which met to discuss the subject on June 8. The Surgeon General was represented at this meeting by Lieutenant Colonel Francis R. Dieuaide, F.A.C.P., Chief of the Tropical Disease Treatment Branch, Medical Consultants Division.

"Sulfa" in Wounds Discontinued

The Army's accumulated experience in wound management does not justify the local use of any chemical agent in a wound as an anti-bacterial agent, according to the

Office of The Surgeon General. The local use of crystalline sulfonamides (sulfa powder) has therefore been discontinued except in the case of serous cavities where its use, while permissible under the direction of the surgeon, is not recommended. This subject is covered by War Department Circular No. 160 as amended by W. D. Circular No. 176, 1945.

Colonel Lueth, Chief of Classification Branch

Lieutenant Colonel Harold C. Lueth, F.A.C.P., of Evanston, Ill., has been assigned as Chief of the Classification Branch, Military Personnel Division, Office of The Surgeon General.

Before coming to the Office of The Surgeon General in February of this year, Colonel Lueth was Liaison Officer for The Surgeon General to the American Medical Association, with headquarters in Chicago—a post which he held for three years. He also served as Consultant in Procurement and Assignment to the War Manpower Commission.

Policy on Assignment of M. C. Officers to Veterans Administration

Additional U. S. Army Medical Corps officers will not be assigned to duty with the Veterans Administration unless they had previously been serving on the staff of that organization, Major General George F. Lull, F.A.C.P., Deputy Surgeon General of the Army has announced.

In outlining this War Department policy, General Lull stated that in the event officers specifically requested service with the Veterans Administration they would be eligible for such assignments.

Promotions in the Army Medical Corps

From Lieutenant Colonel to Colonel:

John Randall McBride (Associate), Hillsboro, Ohio.

From Major to Lieutenant Colonel:

Clifton Harold Berlinghof, F.A.C.P., Binghamton, N. Y.
Sander Cohen, F.A.C.P., Cincinnati, Ohio.
Harold Ellsworth Hathhorn (Associate), Youngstown, Ohio.
Samuel Edward King, F.A.C.P., New York, N. Y.
Isadore Jacob Kwitny (Associate), Indianapolis, Ind.
George William Stuppy, F.A.C.P., Chicago, Ill.

Dr. Leroy E. Burney (Associate) has been given leave from the U. S. Public Health Service as of July 1, 1945, to assume the position of Secretary of the Indiana State Board of Health and State Health Commissioner of Indiana.

Colonel Orpheus J. Bizzozero, F.A.C.P., has been serving with the Army Medical Corps in Italy for a considerable period of time. He will hold the Allied Military Government's health commission for the Milan region, it is announced. He previously supervised medical services at Palermo and became Director of Public Health in Sicily. He later served as a health officer in Rome and received an honorary degree in medicine from the University of Palermo.

The United States Public Health Service has recently issued the National Institute of Health Bulletin No. 183 containing studies of typhus fever.

Captain Lyle J. Roberts, (MC), U. S. Navy, a Fellow of the American College of Physicians, was among medical officers taken prisoner by the Japanese in the Philippines in early 1942. It was not until May of 1945 that the College learned of that misfortune and found out through the wife of one of its other members, also a Japanese prisoner, that Captain Roberts was among the officers and men moved from the Philippines to some prison camp in Manchukuo.

Dr. Hugo T. Engelhardt (Associate), for six years a member of the Department of Medicine at Tulane University School of Medicine, New Orleans, is now associated with the Humble Oil & Refining Company of Houston, Tex., as internist.

Dr. Charles F. McKhann, F.A.C.P., recently Assistant to the President in charge of research at Parke, Davis & Company, Detroit, has been named Professor of Pediatrics at Western Reserve University School of Medicine and Director of Pediatrics at the University Hospital, Cleveland. He succeeds Dr. Henry J. Gerstenberger, who will become Professor Emeritus of Pediatrics beginning with the next school year.

The appointment became effective as of July 1, but Dr. John A. Toomey, F.A.C.P., will remain as Acting Director of Pediatrics at the University Hospitals until September 1. Dr. Toomey will continue at Western Reserve University as Professor of Clinical Pediatrics and Contagious Diseases, and in charge of the Departments of Contagious Diseases at University and City Hospitals.

Dr. McKhann is widely known for his work in pediatrics. He is a graduate of Miami University and holds the degree of Bachelor of Science, Master of Arts and Doctor of Medicine from the University of Cincinnati. He was assistant and instructor in the Harvard Medical School from 1923 to 1930, and Assistant Professor of Pediatrics and Communicable Diseases in the Medical School and the School of Public Health, Harvard University, from 1930 to 1936. From 1935 to 1940 he was Associate Professor at Harvard Medical School and its School of Public Health; and from 1940 to 1943 he was Professor of Pediatrics and Communicable Diseases at the University of Michigan. He was Visiting Professor of Pediatrics at Peiping Union Medical College, Peiping, China, from 1935–1936 on a grant from the Rockefeller Foundation.

In addition to his work as a teacher and administrator, Dr. McKhann is probably best known for his work on the feeding of children and for his work with the fractionization of serums and the use of these serum fractions in the treatment of infectious diseases. He has contributed to several textbooks and is the author of more than fifty scientific papers.

Dr. John M. Swan, F.A.C.P., Rochester, N. Y., is the Executive Secretary of the New York State Committee of the American Society for the Control of Cancer. He still holds a commission as Colonel in the Medical Reserve Corps (inactive) of the Army.

Fifty Per Cent Increase in Poliomyelitis Cases

In the June issue of the National Foundation News it was reported that there is an increase of almost 50 per cent in the number of infantile paralysis cases for the first five months of 1945, as compared to the same period in 1944. A total of 740 cases was reported throughout the United States as of May 26 of this year. The greatest increase has been in the Middle Atlantic States where the number of poliomyelitis cases increased from 43 to 178. In the South Atlantic States there were 106 cases this year compared with 50 last year; the East South Central States, 79 this year, 32 last year; New England States increased from 15 to 30; West North Central

States increased from 30 to 41; East North Central States increased from 41 to 75; West South Central States increased from 110 to 122.

A decrease occurred in the Pacific Coast States and the Mountain States.

Abbott Laboratories Provide Research Foundations

The Abbott Laboratories, North Chicago, Ill., recently announced an appropriation of $50,000 for Research Fellowships in ten universities, $5,000 each to support research in the field of medical products during a five-year period, beginning one year after the end of the war. The universities are given complete control of the results of the research conducted. Neither are they restricted regarding the type or scope of the problem selected within the specified field. Institutions selected include California Institute of Technology, Cornell University, Harvard University, University of Illinois College of Medicine, Massachusetts Institute of Technology, University of Minnesota, Ohio State University, Purdue University, Tulane University of Louisiana and the University of Wisconsin.

Legion of Merit Awards

Commodore William W. Hargrave

Commodore William W. Hargrave, F.A.C.P., (MC), U. S. Navy, formerly of Philadelphia, has been awarded the Legion of Merit, the citation reading: "for exceptionally meritorious conduct in the performance of outstanding services to the government of the United States as medical officer in command of the United States Naval Hospital, Pearl Harbor, T. H., from Aug. 17, 1943 to July 3, 1944 and as medical officer in command of the United States Naval Hospital, Aiea, T. H., from July 4, 1944 to Feb. 9, 1945. A counsellor and director of rare understanding and broad vision, Commodore (then Captain) Hargrave exercised unfailing tact and wisdom in the administration of both hospitals and, applying his special knowledge with skill and judgment, created and maintained exceptionally high standards of professional service to the patients under his command. By his close personal supervision, his sympathetic concern and genuine interest in the individual welfare and morale of personnel, Commodore Hargrave inspired and encouraged the rapid rehabilitation of patients essential to the successful prosecution of the war against Japan."

Lieutenant Colonel Robert E. Lyons, Jr.

Lieutenant Colonel Robert E. Lyons, Jr. (Associate), (MC), AUS, formerly of Shreveport, La., was recently awarded the Legion of Merit for "Services as chief of the medical record division, Eighth Air Force, from July, 1942 to December, 1943. He devised methods of compiling wound and injury data from sick and wounded reports and field medical records which resulted in a complete medical record of Eighth Air Force combat wounds. The major portions of the body receiving wounds were indicated by percentages, representing a total of all wounds. This important record revealed that a large proportion of serious and fatal battle wounds among air crews was caused by relatively low velocity missiles incurred in an area of the body that could be protected by armor. Based on this study, individual armor equipment for the protection of air crew members was developed and standardized throughout the Eighth Air Force. By constant review of medical records, he continually developed new methods of presenting and interpreting statistical data. He charted the geographic incidence and sources of injuries and diseases which resulted in an immediate intensification of the venereal disease program in all areas. He utilized the material in the revised care of flier report to prepare charts and data which contributed greatly to

the reduction of frostbite and anoxia, thereby increasing the training level of combat crews before their shipment to the theater. He further conducted exhaustive research in the development of accurate attribution tables for air crews of heavy bombardment units by reviewing the combat history of hundreds of crew members in each crew position throughout their entire combat careers. After an enormous amount of work and research he completed the report which served as a temporary basis for computing replacement requirements and proved invaluable to the Army Air Forces material and services commands. By his untiring efforts, competent grasp of the situation and high devotion to study he contributed materially to the outstanding success of the aerial offensive against the enemy."

Colonel Cornelius P. Rhoads

Colonel Cornelius P. Rhoads, F.A.C.P., (MC), AUS, formerly of New York City, was awarded the Legion of Merit recently with the following citation: "He developed new methods of diagnosis and treatment for relief of injuries due to toxic chemicals and perfected a compound to counteract the effects of blister gas. At Bushnell, Fla., and San Jose Island, Canal Zone, he established medical testing stations. He also developed equipment for detecting the presence of war gases in air, food and water."

Lieutenant Colonel Isidore A. Feder Receives Bronze Star

Lieutenant Colonel Isidore A. Feder (Associate), (MC), AUS, formerly of Brooklyn, recently received the Bronze Star "for meritorious service in connection with military operations against the enemy as Chief of Medical Service, 45th Evacuation Hospital, Semimobile, from June 17, 1944 to Aug. 1, 1944 in France. Lieutenant Colonel Feder expertly supervised the diagnosis and treatment of numerous medical cases. He displayed keen insight in properly distributing the medical services of officers, nurses and enlisted personnel to insure prompt and adequate treatment of the wounded. By his initiative, professional knowledge and skill, Lieutenant Colonel Feder reflected credit on himself and on the military service."

Dr. Edward Kupka, F.A.C.P., is Medical Director of the Hastings Foundation for Tuberculosis Research, Pasadena, Calif.

Dr. George C. Lockard, F.A.C.P., will represent the University of Maryland School of Medicine; Dr. Robert H. Riley, F.A.C.P., will represent the State Department of Health; and Dr. Victor F. Cullen, F.A.C.P., will represent the Maryland State tuberculosis sanatoriums, on the newly created Council on Medical Care set up by authority vested in the State Board of Health in Maryland to provide consultation and advice in connection with the program to be administered by the Bureau of Medical Services of that State.

Dr. George K. Wharton, F.A.C.P., Kingston, Ont., is now Professor of Clinical Medicine at Queens University, Chief of the Clinical Service on Medicine at Kingston General Hospital and Consultant in Medicine at Hotel Dieu. He is certified by the American Board of Internal Medicine and by the Specialty Board of the Royal College of Physicians and Surgeons of Canada.

Dr. John F. Kenney, F.A.C.P., Pawtucket, has been installed as President of the Rhode Island Medical Society.

Dr. Waller S. Leathers, F.A.C.P., retired on June 30, 1945, as Dean of Vanderbilt University School of Medicine, Nashville. Dr. Leathers had served as Dean and Head of the Department of Preventive Medicine and Public Health since 1928. He was succeeded by Dr. Ernest W. Goodpasture who heretofore had been Associate Dean and Professor of Pathology.

Dr. Edwin J. Simons, F.A.C.P., Swanville, has been elected President of the Minnesota State Medical Association and succeeds Dr. Edward L. Tuohy, F.A.C.P., Duluth, on January 1, 1946. Dr. Benjamin B. Souster, F.A.C.P., St. Paul, was elected Secretary.

American Board of Pediatrics to Hold Examinations

The American Board of Pediatrics will conduct its oral examination at Atlantic City, N. J., Hotel Claridge, December 7–9. The examination was first scheduled for New York City, but had to be changed because hotel reservations were not available. The written examination of the Board will be conducted locally under a monitor on October 19.

Dr. Andrew C. Ivy, F.A.C.P., will supervise the work of research in cancer education at Northwestern University, Chicago, under a grant in aid of $8,500 by the National Advisory Cancer Council. Dr. James H. Means, F.A.C.P., will likewise supervise the study of the relation of steroid hormones to growth and tumors under a grant of $24,500 to Harvard University from the same source. Dr. Leon Schiff, F.A.C.P., will supervise clinical studies of gastric cancer under a grant of $10,000 from the Council to the University of Cincinnati. The total grant to all institutions by the National Advisory Cancer Council is $79,377, the largest amount ever granted at one time by the Council.

Dr. Virgil P. Sydenstricker, F.A.C.P., Professor of Medicine at the University of Georgia School of Medicine, Augusta, is now Chief of the United Nations Relief and Rehabilitation Association's Nutrition Service and is reported still to be aiding patients at the Belsen Concentration Camp in Germany.

Correction

Dr. Paul R. Meyer, Port Arthur, Tex., was honorably discharged from the Army Air Corps as a Lieutenant Colonel rather than as a Captain, as published in the June issue of this journal.

On June 23, 1945, the University of Southern California conferred the honorary degree of Doctor of Science upon Walter L. Treadway, M.D., F.A.C.P., formerly Assistant Surgeon General (1929–38) and Medical Director (Retired), United States Public Health Service.

The War-Time Graduate Medical Meetings

The more active program of the War-Time Graduate Medical Meetings is somewhat suspended during the summer months although this period is used in preparing and organizing the sessions for the early autumn.

Under the chairmanship of Dr. James J. Waring, F.A.C.P., Denver, Zone No. 19, a program was given at the hospital at Camp Carson, Colorado Springs on July 19 including "Surgery of the Sympathetic Nervous System," Dr. Merrill C. Jobe; "Pulmonary Infarction," Dr. R. W. Vines; "Recent Advances in Diabetes," Dr. S. S. Kauvar, F.A.C.P.

In Zone No. 23 a graduate medical meeting will be conducted at the Dibble General Hospital, Menlo Park, California on September 3 including "Diagnosis and Treatment of Arthritis," Dr. S. R. Mettier, F.A.C.P.; "Nephritis," Dr. Leslie L. Bennett.

A review of the activities of the committee for the six months ending June 30, 1945 reveals that over the country there have been 60 individual meetings of 111 sessions and 90 continuation courses of 646 sessions, making a total of 150 meetings and 757 total sessions. These were conducted in 101 army installations, 23 naval installations and 7 at civilian centers. The total cost for this rather extensive program including administration, printing, traveling expenses of the committee and instructors, honoraria to instructors in certain instances and other miscellaneous items amounted to $14,119.01.

Inquiries are received at the executive offices of the committee from time to time from entirely new installations where programs have not been previously conducted. There has been a steady recognition and growing appreciation of the value of this nation-wide effort among the medical officers of our armed forces.

Ten Fellowships in Psychiatry Available at University of Michigan

There are now ten one-year fellowships in Psychiatry available at the University of Michigan. Each will offer an annual stipend of $2,000. These fellowships are under the aegis of the Office of Veteran's Affairs of the State of Michigan. Appointees will be trained at the Neuropsychiatric Institute of the University of Michigan. Candidates must be graduates of a Class A Medical School, and must complete a rotating internship before beginning their fellowship. Applications should be made to Dr. Raymond Waggoner, Professor of Psychiatry, University Hospital, Ann Arbor, Michigan.

MINUTES OF THE BOARD OF REGENTS

Philadelphia, Pa.

June 10, 1945

The regular spring meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters, Philadelphia, June 10, 1945, with President Ernest E. Irons presiding, Mr. E. R. Loveland acting as Secretary, and the following in attendance:

Ernest E. Irons	President
Walter W. Palmer	First Vice President
James J. Waring	Second Vice President
William D. Stroud	Treasurer
George Morris Piersol	Secretary-General

Jonathan C. Meakins	
Hugh J. Morgan	
Charles F. Tenney	
Francis G. Blake	
Roger I. Lee	
Charles T. Stone	
James E. Paullin	
LeRoy H. Sloan	
Maurice C. Pincoffs	Editor, Annals of Internal Medicine
Paul W. Clough	Acting Editor, Annals of Internal Medicine
Chauncey W. Dowden	Chairman, Board of Governors
O. H. Perry Pepper	Chairman, Committee on Finance

The Executive Secretary read abstracted Minutes of the preceding meeting of the Board, which were approved as read.

The Executive Secretary, among the communications, presented the resignation of Dr. Fred W. Wilkerson, F.A.C.P., Montgomery, Governor of the College for Alabama, the resignation being submitted because of illness. President Irons, after consulting the Board, appointed Dr. E. Dice Lineberry, F.A.C.P., Birmingham, as Governor for Alabama to fill out the unexpired term of Dr. Wilkerson, namely, until 1947.

President Irons announced the sudden death of Dr. William W. Herrick, F.A.C.P., New York, N. Y., on June 1. Dr. Herrick had been serving as the member of the Committee on Post-War Planning for Medical Service, and at one time had served as a Regent of the College. President Irons announced the appointment of Dr. Walter W. Palmer, F.A.C.P., New York, N. Y., to succeed Dr. Herrick on the Committee on Post-War Planning for Medical Service.

As a communication, Mr. Loveland reported that due to illness, Dr. Sydney R. Miller, F.A.C.P., Baltimore, resigned some months ago as a member of the Committee on Credentials, and the appointment subsequently by President Irons of Dr. LeRoy H. Sloan, F.A.C.P., Chicago, succeeding Dr. Miller for a term expiring in 1945 or until the next date when appointments are made.

It was suggested by Dr. James E. Paullin that the President send a letter of thanks to Dr. Wilkerson and to Dr. Miller for their valuable service to the College.

The Secretary-General, Dr. George Morris Piersol, reported the deaths of 34 Fellows and 3 Associates since the last meeting of the Board, as follows:

Fellows

*Clendening, Logan	Kansas City, Mo.	January 31, 1945
Confair, William Freas	Benton, Pa.	January 14, 1945
Cotter, Thomas F.	Indiana Harbor, Ind.	March 12, 1945
Dever, Francis Joseph	Bethlehem, Pa.	December 30, 1944
Dibble, John	M.C., U. S. Army	April, 1943
Donald, William M.	Detroit, Mich.	December 20, 1944
Flinn, John W.	Prescott, Ariz.	November 21, 1944
Gorham, Frank D.	St. Louis, Mo.	November 27, 1944
Grant, Brooks Collins	M.C., U. S. Army	January 1, 1945
Grauer, Frank	New York, N. Y.	February 16, 1945
Grill, John C.	Milwaukee, Wis.	March 17, 1945
Hall, William W.	Watertown, N. Y.	January 3, 1945
*Herrick, William W.	New York, N. Y.	June 1, 1945
Irving, Peter	New York, N. Y.	December 28, 1944
Klaus, Emanuel	Cleveland, Ohio	March 21, 1945
Klopp, Henry Irwin	Allentown, Pa.	March 7, 1945

* Former Regents.

Lawrence, Charles H.	Boston, Mass.	March 13, 1945
Luippold, Eugene John	Weehawken, N. J.	December 16, 1944
Mahony, Fergus O.	El Dorado, Ark.	February 6, 1945
Mills, Harlan Page	Phoenix, Ariz.	February 27, 1945
Neal, Frank	Peterborough, Ont.	January 18, 1945
Nicholas, Estes	Portland, Maine	December 12, 1944
Northrup, William	Ionia, Mich.	December 9, 1944
Pepper, John K.	Winston-Salem, N. C.	October 31, 1944
Pudor, Gustav A.	Portland, Maine	March 7, 1945
Purdie, Robert McNair	Houston, Tex.	April 9, 1945
Ricketts, George Allen	Osceola Mills, Pa.	December 6, 1944
Rudy, Abraham	Boston, Mass.	February 19, 1945
Sinclair, Charles George	M.C., U. S. Army	May 3, 1945
Smith, Bertnard	Los Angeles, Calif.	January 23, 1945
Speidel, Frederick George	Louisville, Ky.	October 15, 1944
Warren, Mortimer	Portland, Maine	October 8, 1944
Weissberg, Morris	Brooklyn, N. Y.	March 17, 1945
Winemiller, James Lewis	Great Neck, N. Y.	October 1, 1944

Associates

Smith, Esmonde B.	Brooklyn, N. Y.	February 2, 1945
Talbot, Francis J.	Niagara Falls, N. Y.	November 11, 1944
Willett, Thomas	West Allis, Wis.	February 25, 1945

Dr. Piersol reported the following list of 65 additional Life Members since the the last meeting of the Board, making a grand total of 387 Life Members, of whom 33 are now deceased, leaving a balance of 354 (named in the order of subscription):

Albert F. R. Andresen	Brooklyn, N. Y.
Henry A. Christian	Brookline, Mass.
Erwin D. Funk	Wyomissing, Pa.
George M. Levitas	Westwood, N. J.
Eugene E. Marcovici	New York, N. Y.
Samuel T. Nicholson, Jr.	Pottstown, Pa.
Ralph L. Shanno	Forty Fort, Pa.
Carl Edward Johnson	Morgantown, W. Va.
Frank B. Kelly	Chicago, Ill.
David L. Perry	New Castle, Pa.
Fred John McEwen	Wichita, Kan.
John W. Scott	Lexington, Ky.
V. M. Longmire	Temple, Tex.
Irving J. Sands	Brooklyn, N. Y.
John Albert Bauer	Burlington, Ont., Canada
William S. Reveno	Detroit, Mich.
Irvin R. Fox	Eugene, Ore.
Joseph Kopecky	San Antonio, Tex.
Randolph Lyons	New Orleans, La.
Robert G. McCorkle	San Antonio, Tex.
Thomas P. Sprunt	Baltimore, Md.
Meldrum K. Wylder	Albuquerque, N. M.
Joseph A. Pollia	Los Angeles, Calif.
Fred Sternagel	West Des Moines, Iowa
C. Clyde Sutter	Rochester, N. Y.
Chester Quay Thompson	Omaha, Nebr.

Arthur Christian DeGraff	New York, N. Y.
John Day Garvin	Pittsburgh, Pa.
John E. Nelson	Seattle, Wash.
D. D. Comstock	Los Angeles, Calif.
W. Bernard Yegge	Denver, Colo.
Elliott P. Smart	Murphys, Calif.
Guy D. Callaway	Springfield, Mo.
Thomas Everett Strain	Shreveport, La.
Francis M. Pottenger, Jr.	Monrovia, Calif.
Clarence C. Campman	West Middlesex, Pa.
G. Stirling Landon	San Bernardino, Calif.
Roy A. Ouer	San Diego, Calif.
John H. Fitzgibbon	Portland, Ore.
Henry M. Ray	Pittsburgh, Pa.
Samuel Gitlow	New York, N. Y.
Sigurd W. Johnsen	Passaic, N. J.
Franklin Jesse Nelson	Tulsa, Okla.
Homer A. Ruprecht	Tulsa, Okla.
George R. Maxwell	Morgantown, W. Va.
Henry Nelson Tihen	Wichita, Kan.
Jacob M. Cahan	Philadelphia, Pa.
Irving L. Cabot	Brooklyn, N. Y.
Harold F. Koppe	Dayton, Ohio
Harvey M. Ewing	Montclair, N. J.
Homer D. Cassel	Dayton, Ohio
Otto A. G. Reinhard	Lincoln, Nebr.
Charles H. Parsons	Concord, N. H.
Lawton M. Hartman	York, Pa.
Leopold Shumacker	Chattanooga, Tenn.
Anita M. Muhl	San Diego, Calif.
Donald R. McKay	Buffalo, N. Y.
Wm. Lindsay Miller	Gadsden, Ala.
Samuel G. Shepherd	Philadelphia, Pa.
William D. Stroud	Philadelphia, Pa.
Vernon L. Evans	Aurora, Ill.
Frank Baker Marsh	Salisbury, N. C.
Harry Joseph Friedman	Seattle, Wash.
Mark Alexander Griffin	Asheville, N. C.
William Ray Griffin	Asheville, N. C.

The report of the Secretary-General was unanimously adopted.

Dr. George Morris Piersol, as Chairman of the Committee on Credentials, then presented the following report:

"Since the last meeting of the Board of Regents, Dr. Sydney R. Miller, for many years a member of this Committee, resigned, and Dr. LeRoy H. Sloan was appointed by the President to fill his unexpired term.

"The Committee met yesterday with all members present.

"The Committee unanimously recommends to the Board of Regents the reinstatement of Commander Charles Leroy Denton, Dyersburg, Tenn., to Associateship. Dr. Denton is entitled to a period of ten months more as an Associate following his retirement from active naval service, during which to qualify for Fellowship. The Committee also recommends the reinstatement to Fellowship of Dr. Claude L. Holland, Fairmont, W. Va.; Dr. Holland resigned a few years ago because of ill health

and other problems. His application for reinstatement is accompanied by check to cover past dues. He had been a Fellow for many years."

On motion by Dr. Paullin, seconded by Dr. Palmer, and regularly carried, the above portion of the report of the Committee on Credentials was approved.

Dr. Piersol (continuing): The Committee reviewed the credentials of 150 candidates for Fellowship. Copies of the full list have been distributed to the Board. The summary of the Committee's recommendations are as follows:

Recommended for Advancement to Fellowship	78
Recommended for Election to Direct Fellowship	23
Recommended for Election First to Associateship	9
Deferred for Further Credentials	29
Rejected	11
	150

. . . On motion by Dr. Piersol, seconded and regularly carried, the following list of 101 candidates were elected to Fellowship: (This list was published in the July issue of this journal).

Dr. Piersol (continuing): The Committee reviewed the credentials of 156 candidates for Associateship, and a summary of its recommendations is as follows:

Recommended for Election to Associateship	99
Deferred	29
Rejected	28
	156

To this number must be added the 9 candidates for direct election who are recommended for election first to Associateship, making a total number of recommendations for election to Associateship of 108.

. . . On motion by Dr. Piersol, seconded by Dr. Palmer, and regularly carried, the following 108 candidates were elected to Associateship: (This list was published in the July issue of this journal).

Dr. Piersol (continuing): The Committee makes the following report on the class of Associates elected five years ago, March 31, 1940:

Qualified and Advanced to Fellowship	100
Deceased	2
Deferred, because of Military Service	32
Dropped; Failed to Qualify	10
	144

Five Associates who are practicing physicians have failed to qualify for Fellowship within the five-year maximum term, and in accordance with regulations of the Board of Regents and the By-Laws are recorded as dropped from the Roster. Thirty-three Associates have been granted an extension of time, because of active military service, to qualify for Fellowship following discharge.

Dr. Chauncey W. Dowden, Chairman of the Board of Governors, brought to the attention of the Committee reports and suggestions from the majority of the Governors of the College. These suggestions were discussed at length, especially from the standpoint of the recommendation of the Board of Regents that certification shall

some time in the future become a prerequisite for election to Associateship. A resolution was adopted by the Committee on Credentials to recommend to the Board of Regents the following plan:

(1) Certification shall be a prerequisite for Associateship;
(2) If this rule is adopted, the College shall abandon the five-year maximum Associate term, which will require amendments to the By-Laws;
(3) The specific qualifications for Fellowship shall be revised by the Credentials Committee, subject to approval by the Board of Regents;
(4) The present rules for direct election to Fellowship in special cases shall be retained;
(5) These changes shall become effective as of the date of adoption, and shall apply to all Associates on the Roster at that time, provided they have become certified; other Associates not certified shall remain in the Associate status;
(6) The Committee is cognizant of the effect these changes will have on the age of physicians on admission to the College and the effect also on the postgraduate course program.

. . . Because the last recommendations were subject to discussion, Dr. Piersol moved that the balance of the report of the Committee on Credentials, exclusive of the last recommendations, be adopted. . . .

. . . The motion was seconded by Dr. Waring and passed. . . .

. . . It was moved by Dr. Piersol, seconded by Dr. Lee that the Board of Regents adopt the new recommendations, constituting the latter part of the report of the Committee on Credentials regarding revised requirements for membership. The matter was opened for discussion. . . .

President Irons: There are manifestly certain advantages in the recommendation of the Credentials Committee. There are one or two disadvantages. The first is, in the view of the Chair, that if you take this action you are making a gate for the membership through which members enter the College and delegating the function of gatekeeper to the Board on Internal Medicine, which is separate from the College. It is true the Board works in close harmony with the College, but it is an outside organization, and I doubt the wisdom or the constitutionality of delegating to an outside body who shall be elected a member of the College. Secondly, there is another educational objection. The five-year Associate term is a period during which the young man gets, or should get, the stimulus of College association. His Associateship is one of the things that helps him on his way. The American Board has stimulated progress and education among younger men. The whole attitude of the young man after he leaves his hospital has been changed in many cases. The Associate period of probation is a period of stimulation, during which the young man is likely to be helped to grow by his College associations. If you say to him, "You cannot even look in at the door until after you have been certified," then you take away from him one of the aids that he would have had in accomplishing his passage of his Board examinations. These two objections should be very seriously considered, notwithstanding the fact that there are cogent other reasons submitted in favor of the motion by the Credentials Committee. We ought to have very careful discussion of this matter, because it is fundamental.

Dr. Roger I. Lee: Mr. President, a good many of us are more accustomed to studying things from the printed word than we are from the spoken word. We have had this report read to us. It is very important. It is worthy of most careful consideration, and I myself should doubt very much whether action should be taken at this time. I should like, therefore, to move that this be written up and circularized

now and before the next meeting of this Board, in order to give us plenty of opportunity to study and reflect upon these very fundamental changes.

. . . The previous motion was withdrawn, and Dr. Lee's motion substituted. It was seconded by Dr. Waring and adopted. . . .

. . . Dr. Roger I. Lee, Chairman of the Committee on Public Relations, presented the following report:

"The Committee met on June 9, 1945, at 11:00 a.m., at the College Headquarters. Those present were Drs. Paullin, Irons and Lee.

I. *Resignations:*

The Committee voted to recommend the acceptance of the resignation of Dr. Leon Ashman (Associate), Baltimore, Md.;

Recommended the retention on the Roster of Fellows the name of Dr. Herbert L. Reynolds, F.A.C.P., Atlanta, Ga., with waiver of dues until his recovery and resumption of practice;

Recommended the acceptance of the resignation of Dr. Harry Perry Thomas (Associate), San Antonio, Tex.

II. *Fees and Dues Cases:*

The Committee voted to recommend the waiving of dues on account of illness, until recovery and resumption of work, in the case of one Associate and three Fellows.

III. *Communications:*

Certain communications were received and read. It was voted to recommend the reference to the American Heart Association of the communication of Dr. L. R. McCauley, F.A.C.P., re coronary deaths among physicians;

It was voted to recommend the filing of a resolution by Veterans Affairs Committee of Brooklyn, N. Y., and the filing with thanks of communications from the British Consulate General re Rehabilitation Films and from the National Research Council.

IV. *Delinquent Members:*

It was voted that in accordance with provisions of the By-Laws of the College five delinquent members be informed that their names must be dropped from the Roster unless their dues accounts are brought up to date within a period of sixty days herefrom.

. . . On motion by Dr. Lee, seconded and regularly carried, the recommendations of the Committee were adopted, and the report as a whole was approved. . . .

. . . Dr. Walter W. Palmer, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, reported a meeting by that Committee on June 9, with all members of that Committee present, and with Dr. David P. Barr sitting in on the deliberations of the Committee. He brought certain facts, furnished by the Executive Secretary, to the attention of the Board, including: the 1936 circulation of the journal was 3,627, whereas it is now in excess of 7,400; the College has lost through reduction in Initiation Fees and the waiving of dues of members on active military service something in excess of $25,000.00 annually; the income of the College has been considerably increased through subscriptions to the journal; for instance, the circulation in December, 1941, at the opening of the War, was 5,505, and the circulation for May, 1945, was 7,412, an increase of 1,907 or 34.6%; the advertising income for 1941 was $9,096.12 and for 1944, $13,279.83, an increase of $4,183.71 or 45.9%; the advertising income for 1945 will be materially further increased; increase in circulation has been due, in the opinion of the Committee, to the improvement in the quality of the journal; increases in the advertising rates will go into effect as of July 1, 1945; the cost of publication has increased through the years as follows:

Cost per page—

May, 1936	$7.13
May, 1938	7.48
May, 1940	7.69
May, 1942	8.22
May, 1944	9.18
April, 1945	9.84,

an increase since 1936 of $2.71 per page. The journal is due to come from press about the sixteenth of each month, but the printers have had labor shortage, and the delay has been largely due to the printers, rather than the Editor's Office. An effort will be made to improve this situation. The Committee believed that if the Editor could publish during the year four or five fairly comprehensive good reviews and offer sufficient honoraria for the reviews, the value of the journal would be enhanced. To that end, the Committee recommended that the Editor be authorized to offer an honorarium of $100.00 for each such review, not exceeding five reviews per year.

In closing his report, Dr. Palmer said: "The Committee is impressed with the work of the Editor and the Executive Secretary, and wish to express their keen appreciation."

President Irons called upon the Editor, Dr. Paul W. Clough, for a report.

DR. PAUL W. CLOUGH: I have little to add. We have gotten the ANNALS out without any undue difficulty. The same problems that have been discussed previously are still present—the question of suitable material. The size of the journal has been reduced a little. The current Volume, which will be concluded with the June number, will probably be about one hundred pages shorter than the Volume of a year ago. Material is coming in a little better at the present time, and the quality is a bit better. We have at present enough material in the way of main articles to complete the November number, and somewhat more than enough case reports already accepted to complete that number. In other words, we are publishing about six months after the receipt of manuscripts. Articles which are of active interest and which it is desirable to get into print promptly, usually can be published in about three months. The actual mechanics of getting an article into print following submission of the manuscript to the printer requires about two months. The delay in the appearance of the journal at present is largely due to the printer's difficulties. Manuscripts and Editorials have gone in promptly. Our major deficiency right now is getting adequate book reviews. Some of the members of the Board have helped us out at times in finding reviewers of certain books, but personally I have practically no time to devote to that, and it has been extremely difficult to find competent reviewers.

DR. O. H. PERRY PEPPER: President Truman yesterday appointed a board to declassify secret material in the scientific and technical fields. That may lead to the freeing of a quantity of very excellent work, and it would seem desirable if the ANNALS were to clear its decks, so to speak, for two reasons: first, this material would be new and valuable; secondly, it would be of great service to these men who have done this work and have been prevented from receiving their proper recognition.

. . . On motion seconded and regularly carried, the Editor's report was accepted. . . .

At this point, President Irons asked Colonel Maurice C. Pincoffs to make some remarks.

COLONEL MAURICE C. PINCOFFS: Mr. President, I can only say that the ANNALS have been coming over to our theater and neighboring theaters with reasonable regularity, and these journals (and I include other outstanding clinical journals) have meant a tremendous lot to the men in the smaller hospitals and other medical institutions in the theater. When I left Baltimore I thought the ANNALS would have a

very difficult time as the War went on in finding suitable material, but it seems to me that it has improved rather than retrogressed in any way. I think the motion of thanks to the Acting Editor is certainly fully deserved.

President Irons then called upon Dr. Piersol to present a report on the War-Time Graduate Medical Meetings Committee.

Dr. Piersol, on behalf of the Chairman, Dr. Francis F. Borzell, presented a brief report of the activities of the War-Time Graduate Medical Meetings Committee, emphasizing the continuance of its active program. He also presented a financial report for the period January 1 through May 31, 1945, showing receipts amounting to $23,747.85, represented in contributions by the American College of Physicians, the American College of Surgeons and the American Medical Association, and expenditures of $11,550.63, with a cash balance on May 31, 1945, of $12,197.22. The largest single expenditure for the War-Time Graduate Medical Meetings is the traveling expense account of instructors.

DR. ROGER I. LEE: This Committee has done a very outstanding job, and it deserves the grateful thanks of everybody. It has worked hard and toiled many times with the greatest of difficulties, and I don't want to be too eulogistic, but it would be too bad if there were not something said of earnest praise for its work. I move that the thanks of the Regents be forwarded to the Chairman and the Committee.

. . . The motion was put and unanimously carried. . . .

President Irons called upon Dr. Francis G. Blake to report for the Committee on Fellowships and Awards.

DR. FRANCIS G. BLAKE: The Committee on Fellowships and Awards met on June 9, with Drs. Fitz, Meakins and the Chairman present. The Committee thinks there will be suitable candidates for Research Fellowships during 1946, perhaps both from men being discharged from the Armed Forces and from the usual other sources. The Committee, therefore, presents the recommendation that the American College of Physicians' Research Fellowships be reëstablished in 1946; that $7,500.00 be appropriated for these fellowships, and that the Executive Committee be authorized to make interim appointments on the recommendation of the Committee on Fellowships and Awards. The Committee feels there should be a little more leeway with respect to stipends, particularly in the case of applicants who may be discharged from the Armed Forces, and it recommends that Research Fellowships may range from $1,800.00 to as much as $2,500.00. The reason for suggesting interim appointments bears on the possibility of applications being received from men discharged from the Armed Forces at unstated times during the course of the year. It would seem unfortunate if there had to be a long interim until the next meeting of the Board of Regents for the awarding of Research Fellowships in such cases. If such authority is granted to the Executive Committee, such an interim may be avoided.

. . . The adoption of this recommendation was moved by Dr. Blake, seconded by Dr. Paullin and carried. . . .

DR. BLAKE (continuing): The Committee considered the John Phillips Memorial Award, and recommends that it be reëstablished at such time as the College may hold its next Annual Meeting.

. . . On motion by Dr. Blake, seconded by Dr. Lee, this recommendation was approved. . . .

DR. BLAKE (continuing): The Committee recommends that $25,000.00 be appropriated for 1946 for Clinical Fellowships in Internal Medicine, available for Fellows and Associates and prospective candidates for Associateship honorably discharged from the Armed Forces; that these fellowships be limited to a term of one year, and shall not be renewable; that the Executive Committee be authorized to make interim appointments on the recommendation of the Committee on Fellowships and Awards. These Clinical Fellowships should be established in Internal Medicine, organized by

the College for the assistance of men coming out of the Armed Forces. There are a great many of them who at the present time have indicated they would like either one or two years' training experience in Internal Medicine. Many indicated they would like three months, six months, or nine months of training. The Committee realizes that any such undertaking would probably interest particularly the younger group of officers who might be considered as potential candidates for Associateship, but in addition to that, if College money is to be used for this purpose, it also should be available for Associates, if there is an occasional Associate who would like to take advantage of it—also any Fellow, although it is not thought by the Committee there will be many applicants from that group. It is realized that this will require a fair amount of money, which probably could not be appropriated from current income, but would have to be considered as a sum to be appropriated from capital funds.

It was also suggested by the Committee that the Officers of the College might possibly consider this a nucleus contribution from the College and might approach the Foundations to see whether they would be willing to match this amount for this purpose. I move the adoption of the recommendations.

PRESIDENT IRONS: A matter of similar character will come up in the report of the Committee on Post-War Planning for Medical Service. It would be appropriate to discuss the two together, and to accept your motion and to take a later vote on it, after discussion of a forthcoming report.

DR. BLAKE: That will be acceptable to the Committee. I move then the acceptance of the report as a whole, excluding the last recommendation until further vote is taken.

. . . The motion was seconded by Dr. Paullin and unanimously carried. . . .

President Irons called upon the Chairman of the Board of Governors, Dr. Chauncey W. Dowden.

Dr. Dowden reported that he had circularized the Governors, asking for expressions of opinion upon the question of certification as a prerequisite for Associateship, the tenure of office for Governors, membership credit for candidates who have had special training while in Service, and post-war activities of the College. He suggested that he and/or the Executive Secretary obtain enough copies of the American Board of Internal Medicine literature concerning purposes, regulations, etc., to distribute to every member of the Board of Governors. He proposed to send a communication to the Governors again, asking them to study more in detail the regulations of the American Board of Internal Medicine, so that they can discuss the whole matter of certification more intelligently when they are permitted next to have a meeting.

Dr. James J. Waring presented a report on the American Board of Internal Medicine in the absence of the Chairman, Dr. Reginald Fitz. The report revealed the Board has a surplus of approximately $51,000.00. The Board has already reduced the examination fees and has reduced its expenditures. Guest examiners are given a small honorarium. The Board may consider further reduction in the fees in the future, because it wants to maintain only a respectable and safe reserve.

President Irons reminded the Board that the American College of Physicians needs to make two appointments to the Board. Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was nominated and elected a member of the Board for term expiring 1947, filling the unexpired term of Dr. Frederic M. Hanes, F.A.C.P., Durham, N. C., resigned; Dr. Truman G. Schnabel, F.A.C.P., Philadelphia, Pa., was nominated and elected to succeed Dr. David P. Barr, F.A.C.P., New York, N. Y., whose term expires June 30, 1945. Dr. Schnabel was elected for a term of three years, to 1948.

The suggestion was made by Dr. Jonathan C. Meakins that the American Board of Internal Medicine consider the possibility of creating some additional Clinical Fellowships, along the same line as proposed by the American College of Physicians.

President Irons called upon Dr. Roger I. Lee, as Chairman, to present the report of the Committee on Educational Policy.

DR. ROGER I. LEE: This Committee met on June 9 with General Morgan, Dr. Irons and the Chairman present, and with Dr. James J. Waring of the Governors' Advisory Committee on Postgraduate Courses. The Committee also had the advice of Doctors Paullin, Meakins and Barr, and of the Executive Secretary, Mr. Loveland.

The Advisory Committee on Postgraduate Courses, which is a Committee of the Board of Governors, has the responsibility of selecting courses to be given, subject to the approval of the Committee on Educational Policy and the Board of Regents. The Committee voted to recommend that the Board of Regents approve the following program of courses for the autumn of 1945:

Course No. 1, *Allergy*—Roosevelt Hospital, New York, N. Y.
Dr. Robert A. Cooke, Director
(one week—October 8–13, 1945)

Course No. 2, *Internal Medicine*—University of Michigan Medical School, Ann Arbor
Dr. Cyrus C. Sturgis, Director
(two weeks—October 15–27, 1945)

Course No. 3, *General Medicine*—University of Oregon Medical School, Portland
Dr. Homer P. Rush, Director
(one week—October 29–November 3, 1945)

Course No. 4, *Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease*—Massachusetts General Hospital, Boston, Mass.
Dr. Paul D. White, Director
(one week—November 5–10, 1945)

Course No. 5, *Endocrinology*—University of Illinois College of Medicine, Chicago, Ill.
Dr. Willard O. Thompson, Director
(one week—November 5–10, 1945)

Course No. 6, *Gastro-enterology*—University of Chicago, Chicago, Ill.
Dr. Walter L. Palmer, Director
(one week—November 12–17, 1945)

Course No. 7, *Advanced Cardiology*—Philadelphia General Hospital, Philadelphia, Pa.
Dr. Thomas M. McMillan, Director
(one week—November 26–December 1, 1945)

At the present time some men who are capable of directing excellent courses are unable to make positive commitments. Consequently, there may be developed other courses, for which a mail vote may be necessary.

After considerable discussion, the Committee voted to recommend through the Finance Committee that the Regents empower the President and Secretary-General to explore the possibility of securing an individual to act as the Educational Director under the Executive Secretary. The Committee feels that a tremendous increase in the various activities of the College's educational program is to be anticipated. The Executive Secretary carries the whole burden at the present time. His one-time assistant has departed. When the Annual Sessions are once more resumed, the executive work will be greatly increased.

. . . Commenting on the report, Dr. Lee added: "It was the feeling of this Committee and of the group that met with the Committee—the idea was initiated by the Executive Secretary—that the College is definitely pointing toward increasing activities along educational lines all the time, and with the cessation of hostilities, there will

be a tremendous increase in these courses. It would be a step in the right direction if a man could be found to add to the staff to act as director of the educational activities of the College. . . . If the College were to embark upon this program it must face a real expense. This Educational Director would, of course, require a secretary and equipment, and he would require an expense account for travel, because one of the important things for him to do would be to get around the country, planning and carrying out the program. The Committee does not want the Board of Regents to feel that this can be done cheaply—it may not cost much for the balance of this year, but in time it would be a real expense, probably over $10,000.00 annually. The Committee feels there is a definite trend in the College to make its educational activities a very prominent feature. We ought to get started in organizing this educational activity as early as possible. Mr. Loveland has done the work of this Educational Director and has done it extraordinarily well. He likes it and that is probably one of the reasons why it has been done so well. However, the Committee looks forward to the time when the Annual Sessions may be resumed, and those Annual Sessions and programs create a great deal of extra work for the Executive Secretary and his staff. If this proposal is approved and if a suitable Educational Director can be located, the Board could authorize his appointment through the Executive Committee, without having to wait until the next meeting of this Board in December."

Colonel Maurice C. Pincoffs: There is in the overseas medical profession a tremendous interest in what they may look forward to in regard to postgraduate activities after they get home. A great body of doctors are specializing in diseases of certain age periods, and there will be a demand for postgraduate courses, exceeding anything that we have experienced in the past. We should be prepared for that and should provide for a great expansion of the College activities in that direction. The College has had experience in this field, and it is in contact with all the educational facilities of the country. I am sure it has a great opportunity to meet what will really be an emergency in postgraduate education.

Dr. Pepper (as Chairman of the Committee on Finance): The principal of our Endowment Fund cannot be touched, only the income can be included in our annual surpluses. If we undertake all of the activities proposed at this meeting, we shall probably exceed our surplus. We estimated a surplus of $10,000.00 for the current year, and this may reach as much as $18,000.00, since we were not permitted to hold the annual combined meeting of the Governors and Regents. On the other hand, with the end of the War, our expenditures in some directions will be decreased and our income in other directions considerably increased.

Mr. E. R. Loveland: If such an officer is added to the College staff, I believe he could be of great service, not only in connection with the courses, but also in connection with our program for post-war planning, and also in connection with the program of the Committee on Fellowships and Awards. It would certainly be worth while to follow up the accomplishments of our Research Fellows, and possibly to keep some close contact with the proposed Clinical Fellows.

. . . On motion by Dr. Lee, seconded by Dr. Stroud, and unanimously passed, the report of the Committee on Educational Policy was approved as a whole.

The Chairman called for the report of the Committee on Post-War Planning for Medical Service, Dr. Piersol, Chairman.

Dr. Piersol: Mr. Chairman, the meetings of the Committee on Post-War Planning have been held in Chicago during the past year, with one or more members representing the College present. The Central Committee has been enlarged by the addition of certain other agencies, such as the American Hospital Association, the American Catholic Hospital Association, the Veterans Administration, the Army, Navy and Public Health Service. The meetings have been held largely at the headquarters of the American Medical Association, which is not only a central location, but that

organization has the facilities to conduct these meetings expeditiously and effectively. The various topics brought before the Committee have a national interest of wide application. It seems to the College Committee that the chief function of the Central Committee has been that of an advisory one, not actually doing many things, but directing and advising in their doing. Its activities and deliberations have made it possible for the leading national medical societies and agencies of this country to coöperate in a way which never before has been done, and to present a united front, as it were, on national problems of interest and important problems that are much too complex and involved for any single group to direct. It is the feeling of the members of this Committee that the Central Committee has really accomplished a very important and outstanding work. One of the most concrete things that has been done to date has been the establishment of a central bureau of information, which has available data by which it can give helpful suggestions to returning Medical Officers, both concerning educational possibilities and placement opportunities. The Central Committee does not intend to direct these men specifically, but has available the data desired. The efforts of the Central Committee have been directed toward utilizing wherever possible local agencies, rather than attempting to direct individual activity through the central group.

The College Committee met on June 9 and discussed many of the subjects which have already been taken up by the Committee on Fellowships and Awards and the Committee on Educational Policy, and curiously enough, and independent of those Committees, has arrived at much the same conclusions. We feel that the role of the College in the post-war medical period must be extended. We are convinced, from a study of questionnaires sent out to Medical Officers in the field, that the returning physicians want not generalities, but concrete suggestions as to the possibilities and plans for post-war medical training. In order to bring that about, the College should take a much more extensive and definite interest in this matter than heretofore; it should establish a fund adequate to carry on this work; its efforts to raise such a fund might well be supplemented by going to the Foundations and possibly certain commercial organizations, notably the manufacturers of drugs and medical equipment, who would welcome the opportunity to participate in this undertaking. We feel confident that should we embark on a definite program and lay it before such organizations, showing that we have ourselves appropriated a substantial sum of money, we could rapidly increase the funds available and enhance the results obtained. It is our belief that the activities of the College toward its members should be of a very personal character, that we should be in a position to offer them a personal service, in addition to anything that the Central Committee might be able to offer, that we should be in a position to advise them on such matters as residencies, opportunities for research, and even possibilities for locations, if these members are returning and are uncertain as to what they should do. Furthermore, the College should continue in this educational field, to expand and to enlarge its short courses and other postgraduate activities, particularly in those specialties concerned with Internal Medicine. In order to implement these activities, there should be set in motion some machinery by which there could be a coöperative effort on the part of the Committee and of the Regents to cover the entire field of post-war medical planning. As you have already heard, the reports from the Committee on Fellowships and Awards and of the Committee on Educational Policy are in principle essentially the same as this report we are now presenting. To bring this program to fruition, steps should be taken to appoint someone, either part or full-time, to act as Educational Director, and to conduct the advisory activities that are contemplated. In order to make this possible, the Committee passed a resolution to recommend to the Regents that this plan be put into operation and to implement it, the Regents authorize an allocation of a sum of $25,000.00. I move the adoption of the report.

. . . The motion was seconded by General Morgan and opened for discussion. . . .

The discussion was directed toward clarifying and synchronizing the various recommendations of the Committee on Fellowships and Awards, the Committee on Educational Policy and Committee on Post-War Planning for Medical Service. There was general insistence that the program be immediately organized and not delayed for months to come. There was also insistence that an appropriation for administration be made separate from an appropriation for the program of fellowships and educational activities.

President Irons asked Dr. Piersol to further clarify his original recommendations for records.

Dr. Piersol: "The Committee recommends the approval of the Board of Regents of the above educational plan, which includes the establishment of funds for training, the establishment of advisory personal service to help our Fellows and Associates in the matter of obtaining residencies, research or clinical fellowships, or advice as to their future locations, and an expansion of the short courses, particularly with reference to those courses in certain specialties. In order to carry out the activity, there should be appointed a full or part-time Educational Director under the Executive Secretary to carry on this work, as a coördinated program."

. . . Dr. Piersol's motion and the one outstanding by Dr. Blake at the end of his report were amended and combined, providing that $10,000.00 be appropriated for administration and $25,000.00 be appropriated for Clinical Fellowships, and the motion was unanimously passed. . . .

Numerous members of the Board emphasized the need for coördination of the efforts of all of these activities, and Dr. Piersol, in particular, as Chairman of the Committee on Post-War Planning for Medical Service, emphasized the recommendation that the entire educational program be carried out through the coöperative effort of all three Committees.

On motion by Dr. Piersol, seconded and regularly carried, it was

Resolved, that the Chairmen of the three Committees—Committee on Fellowships and Awards, Committee on Educational Policy and the Committee on Post-War Planning for Medical Service—shall draw up a concrete, specific educational program to implement the resolutions already adopted.

Dr. Meakins: Do you not think it is apparent that the time has arrived for the Board of Regents to appoint a Committee to take over all educational activities of these three Committees, irrespective of war or peace, and to remove from these other three Committees all activities dealing with educational training?

President Irons: The Chair is not quite clear as to what other implications might come out of such a change. He is inclined to think Dr. Piersol's motion to have the three Chairmen meet and draw up their program is as far as we should go at this point.

Dr. Meakins: I concur.

Luncheon Recess

President Irons, resuming the meeting, called for the report of the House Committee.

Dr. William D. Stroud, Chairman of the House Committee, had nothing of significance to report. He said the maintenance of the building and grounds in fine condition is visible to all; installation of a new heating boiler proved not only necessary, but a good and economical investment, because the College had had adequate fuel under current restrictions for the past winter. The adjoining property, owned by the College, is under lease at a good rental until May 31, 1946.

The report was received with thanks.

President Irons then asked for the report of the Committee on Finance, Dr. O. H. Perry Pepper, Chairman.

DR. PEPPER: The Finance Committee met on June 9, 1945, at the College Headquarters; Drs. Stone, Stroud, Tenney and Pepper and the Executive Secretary being present.

(1) The Committee presents to the Regents in printed form the details of the Employees' Retirement Plan, drawn up by the attorney of the College and the insurance company.

The Committee recommends that the Regents rescind previous resolutions on this subject and adopt this printed document, thus legalizing all conditions of the Plan.

(2) The Committee reviewed the financial status of the College, and considers the situation satisfactory.

There is an estimated surplus of $10,330.00 for 1945, which will probably be increased by the failure to expend an item of $7,500.00 in the budget for an annual meeting of the Officers, Regents and Governors.

Factors influencing the situation include: (a) a material increase in income from the ANNALS; (b) possible increase in costs of clerical and secretarial salaries in the Headquarters' staff; (c) possible cancellation of subscriptions to the ANNALS by the Armed Forces; (d) unforeseen expenditures.

(3) The Committee has approved suggestion of Drexel & Co. for certain changes in investments and for the investment of uninvested funds. When these are carried out, the College will have more than 50% of its funds in bonds, 32% in common stocks, and 18% in preferred stocks. The Committee considers this ratio satisfactory.

According to Article VIII of the By-Laws the Regents must approve securities purchased for the Endowment Fund. The Committee requests approval of the purchase for the Endowment Fund of approximately 16,000 United States Savings Bonds, Series G, 2½s.

. . . By resolution regularly passed, the report was approved and adopted. . . .

Dr. Stroud, Treasurer, presented the following report:

"A summary of the financial operations of the College for 1945 has already been submitted by the Committee on Finance. The accounts of the College for 1944 were audited by a public accountant and his signed report has been inserted in the Minutes of this Board. The net operating surplus for 1944 was $23,628.25, all of which is in the Endowment Fund with the exception of $609.40.

"The book value or cost price and the present market price of securities held by the College are as follows:

	Book Value	*Market Value* *
General Fund	$134,389.10	$145,616.25
Endowment Fund	167,519.78	191,893.75
	$301,908.88	$337,510.00
Total Appreciation	35,601.12	
	$337,510.00	$337,510.00

* May 17, 1945.

. . . The Treasurer's report, by resolution, was accepted, and the Executive Secretary distributed the annual financial statements as prepared by the Auditor for the year 1944.

President Irons asked for reports from any other Committees that had not previously been called upon.

Dr. Stroud reported on the Rheumatic Fever Council of the American Heart Association. Contributions made by various groups go to the American Heart Association, with the understanding that they will be used for the work of the Rheumatic Fever Council. Thus far approximately $25,000.00 had been raised, and the American Legion had been recently approached concerning a sizeable contribution for this work. The Rehabilitation Committee of the American Legion Committee had recommended that the Finance Committee of that organization appropriate $25,000.00 toward this work, which, if approved, will bring the funds raised to $50,000.00 toward the original aim of $100,000.00. Dr. Stroud stated that the members of the Rheumatic Fever Council are outstanding men in the field, and that they have very definite plans for attacking that problem. Insurance companies, having found that 50 per cent of their cardiovascular claims are due to rheumatic heart disease, have become interested in the problem and have organized a foundation for research. The only way in which they can use their funds, in justice to their policy holders, is for research, and Dr. Stroud expressed the belief that their foundation for research will probably have $500,000.00 appropriated for research projects in rheumatic fever.

President Irons inquired concerning the present status of the Conference Committee on Graduate Training in Medicine.

Dr. LeRoy H. Sloan, a representative of the College on that Committee, stated that there has been very little contact for some time, but that a notice of a meeting had been received by him. The purpose of this Conference Committee is to confer with like representatives from the American Board of Internal Medicine and of the Council on Medical Education and Hospitals of the American Medical Association.

President Irons then inquired about the propriety of discontinuing representation by the College on the Advisory Council on Medical Education.

On motion by Dr. Paullin, seconded by Dr. Palmer, and regularly carried, it was

RESOLVED, that the American College of Physicians discontinue its representation on the Advisory Council on Medical Education.

Mentioned for discussion were future plans for the College, including Regional and local meetings, meetings of the Board of Governors and the Board of Regents, the post-war Annual Session and Convocation, and the election and installation of New Officers, Regents and Governors.

The Executive Secretary desired to obtain the reactions of the Regents on the various problems, to get authority of the Board to go ahead if restrictions are lifted. He pointed out that a great host of the members are anxious for the return not only of the Regional Meetings but of the Annual Sessions. He pointed out further that it takes time to consummate the arrangements, both for Regional Meetings and for the Annual Session.

The general attitude was that nothing could be done while present restrictions are in force, and that the ban would not be lifted before the next meeting of the Board of Regents.

Dr. O. H. Perry Pepper resigned as a member and as Chairman of the Committee on Finance, June 10, 1945; President Ernest E. Irons appointed Dr. Roger I.

Lee to fill out his unexpired term until 1946 and appointed Dr. Charles F. Tenney as Chairman of the Committee; the Committee now consisting of:

Charles F. Tenney, Chairman
Roger I. Lee
Charles T. Stone

There followed a discussion of when the next meeting of the Board of Regents should be held. The matter was left to the decision of the Executive Committee, with the suggestion the meeting might be held in November.

Adjournment

Attest: EDWARD R. LOVELAND,
Secretary

OBITUARIES

DR. WILLIAM WORTHINGTON HERRICK

Dr. William Worthington Herrick died suddenly on June 1, 1945, at the age of sixty-six. He was born at Sherman, Connecticut, February 19, 1879. His father, Edward Pierpont Herrick, was a clergyman. He received the degrees of A.B. in 1902 and M.D. in 1905 from Yale University. He served as intern at St. Luke's Hospital, New York. He joined the faculty of Columbia College of Physicians and Surgeons in 1908, and advanced to Professor of Clinical Medicine, an appointment held for many years. His hospital positions were: Attending Physician, Presbyterian Hospital and Sloane Hospital for Women; Consulting Physician, Woman's Beekman Street, Mary McClellan (Cambridge), Vassar Brothers (Poughkeepsie), Elizabeth A. Horton Memorial (Middletown), Mount Vernon, Goshen, St. Agnes (White Plains), White Plains, Stamford (Connecticut), Sharon (Connecticut), Greenwich (Connecticut), Nassau (Mineola) Hospitals, and New York Infirmary for Women and Children. He was a member of the Board of Trustees, Trudeau Sanatorium, New York State and County Medical Societies and the American Medical Association. He assumed office of President in the New York Academy of Medicine, January 1, 1945, was a Fellow of the American College of Physicians since 1919, and had been serving recently as a member of the Committee on Postwar Planning for Medical Service, and at one time was a Regent of the College. He was a Diplomate of the American Board of Internal Medicine and Editor-in-Chief of Nelson's Loose Leaf System.

Clinical medicine was Dr. Herrick's passion. And he was most successful in its practice. Always keen in observation, a rare sense of values, a wealth of experience on which to draw and a highly developed power of integration placed him among the outstanding men in medicine both in New York City and the country. He loved to make rounds with students and interns. The students and interns loved to have him. Clinical pathological conferences for the students were his special delight and no one on the staff could surpass him in this exercise.

Dr. Herrick had many interests outside the practice of medicine. He was fond of music, in fact had an organ installed in his home in Sharon, Connecticut. He played a good game of golf. He built furniture in his shop and was no mean wood carver. A large farm occupied much of his time and interest. In Sharon, his summer home, he was not just a "city folk" but took part in the community life and was sincerely interested in the welfare of the town's citizens. This interest was lifelong for in his early youth in the small village of Sherman, where his father was minister, he came to know the country people and had the greatest admiration for their simplicity, honesty and forthrightness, all characteristics preëminent in himself.

Bill Herrick was a modest man. He was quiet, serious and reserved although the humorous side of life never escaped him. His opinions were expressed in few but carefully chosen words. He had the respect and admiration of his colleagues and associates and the affection of his friends. The College has lost one of its distinguished Fellows.

WALTER W. PALMER, M.D., F.A.C.P.,
1st Vice President, A.C.P.

COLONEL CHARLES GEORGE SINCLAIR

Colonel Charles George Sinclair, Medical Corps, U. S. A., Fellow of the American College of Physicians, died at Percy Jones General Hospital, Battle Creek, Michigan, May 3, 1945. Burial with full military honors was at Arlington National Cemetery, May 8, 1945.

Colonel Sinclair was born November 12, 1889 in Parkdale, Ontario, moving to Port Huron, Michigan, in 1892.

Education—B.S. 1912, M.D. 1914, University of Michigan; Assistant in Hygiene, University of Michigan, 1911–13; Internship, general, Providence Hospital, Washington, D. C. 1914–1915; Internship, communicable diseases, Willard Parker Hospital, New York City, 1922; Graduate, Army Medical School Basic Course, 1916; and Advanced Course in Preventive Medicine, 1921.

Military service—1st Lt., M.R.C., 1915; 1st Lt., M.C., 1916; advanced through the grades to Colonel, 1942; Temporary Colonel, 1941; Mexican Punitive Expedition, 1916; American Expeditionary Forces, France and Germany, June 1917 to October 1919. He was with the first troop convoy to France in 1917 and was battalion surgeon, 16th Infantry, which suffered the first battle casualties, November 3, 1917.

He served through World War I with the First Division and was commanding officer of the First Sanitary train in the Aisne-Marne, Montedier, Noyon, St. Mihiel, and Meuse-Argonne offensives. He was senior laboratory officer at Savenay, France, and of the base laboratory at Brest, France.

At various times on the instructional staff of the Army Medical School, including—Instructor in Pathology, 1925–27, Instructor in Bacteriology, 1927–30, and Instructor in Microbiology, 1925–30; tours of duty included Chief of Laboratory Service, 1925–27, Walter Reed General Hospital; Chief of Laboratory Service, 1933–35, Tripler General Hospital, Honolulu; Chief of Laboratory Service, 1935–40, Station Hospital, Fort Sam Houston; and Director of Preventive Medicine and Clinical Pathology, Army Medical School, 1940–42; Surgeon and Commanding Officer, Station Hospital, Camp Hood, Texas, 1942; Commanding Officer, Sixth Service Command Laboratory and Service Command epidemiologist, 1942 until his death.

In addition to several articles in medical journals he contributed to "Laboratory Methods of the U. S. Army," Lea & Febiger 1929; the section

on Bacteriology, War Department Technical Manual, "Methods for Laboratory Technicians," 1941; author of "Microbiology and Pathology," a textbook for student nurses, F. A. Davis Co. (six editions).

Colonel Sinclair was the son of George and Margaret Jane Sinclair, deceased. He is survived by his widow, Margaret E. Sinclair, two stepdaughters, Mrs. John Campbell and Mrs. Martin Fennell, and two sisters, Dr. Elizabeth S. Peck (Mrs. John P.) instructor at Berea College, Kentucky, and Miss Olive V. Sinclair, instructor at Port Huron Junior College, Michigan.

During his nearly thirty years of Army service he occupied many key positions with great credit to himself and to the military service. In failing health from malignant disease for over two years he continued to fulfill his duty in the Sixth Service Command in an exceptional manner until shortly before his death.

FROM THE OFFICE OF THE SURGEON GENERAL,
U. S. ARMY